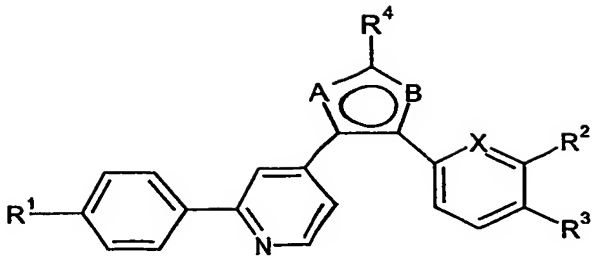
Compounds

This invention relates to novel aminothiazole derivatives which are inhibitors of the transforming growth factor, ("TGF")-ß signalling pathway, in particular, the phosphorylation of smad2 or smad3 by the TGF-β type I or activin-like kinase ("ALK")-5 receptor, methods for their preparation and their use in medicine, specifically in the treatment and prevention of a disease state mediated by this pathway.

TGF-β1 is the prototypic member of a family of cytokines including the TGF-βs, activins, inhibins, bone morphogenetic proteins and Müllerian-inhibiting substance, that signal through a family of single transmembrane serine/threonine kinase receptors. These receptors can be divided into two classes, the type I or activin like kinase (ALK) receptors and type II receptors. The ALK receptors are distinguished from the type II receptors in that the ALK receptors (a) lack the serine/threonine rich intracellular tail, (b) possess serine/threonine kinase domains that are very homologous between type I receptors, and (c) share a common sequence motif called the GS domain, consisting of a region rich in glycine and serine residues. The GS domain is at the amino terminal end of the intracellular kinase domain and is critical for activation by the type II receptor. Several studies have shown that TGF-β signalling requires both the ALK and type II receptors. Specifically, the type II receptor phosphorylates the GS domain of the type I receptor for TGF-β, ALK5, in the presence of TGF-β. The ALK5, in turn, phosphorylates the cytoplasmic proteins smad2 and smad3 at two carboxy terminal serines. The phosphorylated smad proteins translocate into the nucleus and activate genes that contribute to the production of extracellular matrix. Therefore, preferred compounds of this invention are selective in that they inhibit the type I receptor and thus matrix production.

Surprisingly, it has now been discovered that a class of aminothiazole derivatives function as potent and selective non-peptide inhibitors of ALK5 kinase.

According to a first aspect, the invention provides a compound of formula (I), a pharmaceutically acceptable salt, solvate or derivative thereof:



(I)

wherein

either A is S and B is N, or A is N and B is S;

X is N or CH;

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo, cyano, perfluoro C_{1-6}alkyl, perfluoroC_{1-6}alkoxy, $-NR^5R^6$, $-(CH_2)_nNR^5R^6$, $-O(CH_2)_nOR^7$, $-O(CH_2)_n$-Het, $-O(CH_2)_nNR^5R^6$, $-CONR^5R^6$, $-CO(CH_2)_nNR^5R^6$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NR^5SO_2R^7$, $-NR^5COR^7$ and $-O(CH_2)_nCONR^5R^6$;

R^2 is hydrogen, C_{1-6}alkyl, halo, cyano or perfluoroC_{1-6}alkyl;

R^3 is hydrogen or halo;

R^4 is $-NH_2$;

where

R^5 and R^6 are independently selected from hydrogen; Het; C_{3-6}cycloalkyl optionally substituted by C_{1-6}alkyl; or by C_{1-6}alkyl optionally substituted by Het, alkoxy, cyano or $-NR^aR^b$ (where R^a and R^b which may the same or different are hydrogen or C_{1-6}alkyl, or R^a and R^b together with the nitrogen atom to which they are attached may form a 4,5 or 6-membered saturated ring); or R^5 and R^6 together with the nitrogen atom to which they are attached form a 3, 4, 5, 6 or 7-membered saturated or unsaturated ring which may contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more substituents selected from halo (such as fluoro, chloro, bromo), cyano, $-CF_3$, hydroxy, $-OCF_3$, C_{1-6}alkyl and C_{1-6}alkoxy;

R^7 is hydrogen or C_{1-6}alkyl;

Het is a 5 or 6-membered C-linked heterocyclyl group which may be saturated, unsaturated or aromatic; which may contain one or more heteroatoms selected from N, S or O and which may be substituted by C_{1-6}alkyl; and

n is 1-4;

with the proviso that the compound of formula (I) is not:

5-[2-(4-chlorophenyl)pyridin-4-yl]-4-pyridin-2-yl-1,3-thiazol-2-amine;

5-[2-(4-methoxyphenyl)pyridin-4-yl]-4-pyridin-2-yl-1,3-thiazol-2-amine;

5-[2-(4-fluorophenyl)pyridin-4-yl]-4-pyridin-2-yl-1,3-thiazol-2-amine;
5-[2-(4-ethylphenyl)pyridin-4-yl]-4-pyridin-2-yl-1,3-thiazol-2-amine; or
5-[2-(4-ethoxyphenyl)pyridin-4-yl]-4-pyridin-2-yl-1,3-thiazol-2-amine.

The term "C_{1-6}alkyl" as used herein, whether on its own or as part of a group, refers to a straight or branched chain saturated aliphatic hydrocarbon radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl and hexyl.

The term "alkenyl" as a group or part of a group refers to a straight or branched chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number(s) of carbon atoms. References to "alkenyl" groups include groups which may be in the E- or Z-form or mixtures thereof.

The term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy.

The term "perfluoroalkyl" as used herein includes compounds such as trifluoromethyl.

The term "perfluoroalkoxy" as used herein includes compounds such as trifluoromethoxy.

The terms "halo" or "halogen" are used interchangeably herein to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "heterocyclyl" as used herein includes cyclic groups containing 5 to 7 ring-atoms up to 4 of which may be hetero-atoms such as nitrogen, oxygen and sulfur, and may be saturated, unsaturated or aromatic. Examples of heterocyclyl groups are furyl, thienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, dioxolanyl, oxazolyl, thiazolyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyranyl, pyridyl, piperidinyl, dioxanyl, morpholino, dithianyl, thiomorpholino, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, sulfolanyl, tetrazolyl, triazinyl, azepinyl, oxazepinyl, thiazepinyl, diazepinyl and

thiazolinyl. In addition, the term heterocyclyl includes fused heterocyclyl groups, for example benzimidazolyl, benzoxazolyl, imidazopyridinyl, benzoxazinyl, benzothiazinyl, oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, dihydroquinazolinyl, benzothiazolyl, phthalimido, benzofuranyl, benzodiazepinyl, indolyl and isoindolyl.

Preferably X is N.

Preferably R^1 is $-NR^5R^6$, $-(CH_2)_nNR^5R^6$, $-O(CH_2)_n$-Het (wherein Het is preferably imidazolyl or oxazolyl), $-O(CH_2)_nNR^5R^6$, $-CONR^5R^6$, $-SO_2R^7$ or $-O(CH_2)_nCONR^5R^6$.

Preferably R^5 and R^6 are independently selected from hydrogen; Het (preferably tetrahydropyranyl); C_{3-6}cycloalkyl optionally substituted by C_{1-6}alkyl; or by C_{1-6}alkyl optionally substituted by Het (preferably furyl), alkoxy, cyano or $-NR^aR^b$ (where R^a and R^b which may the same or different are hydrogen or C_{1-6}alkyl, or R^a and R^b together with the nitrogen atom to which they are attached may form a 4, 5 or 6-membered saturated ring); or R^5 and R^6 together with the atom to which they are attached form a morpholine, piperidine, pyrrolidine or piperazine ring, each of which may be substituted by halo (such as fluoro, chloro, bromo), cyano, $-CF_3$, hydroxy, $-OCF_3$, C_{1-4}alkyl or C_{1-4}alkoxy.

More preferably R^1 is morpholin-4-yl, methanesulfonyl, 4-ethylpiperazin-1-yl, (morpholin-4-yl)carbonyl, (tetrahydropyran-4-yl)-aminocarbonyl, (morpholin-4-yl)methyl, aminocarbonylmethyloxy, 2-(pyrrolidin-1-yl)-ethoxy, (1-methyl-imidazol-4-yl)methyloxy, ethanesulfonyl, 4-(1-ethyl-piperazin-4-yl)carbonyl, (morpholin-4-yl)carbonylmethyloxy, (pyrolidin-1-yl)methyl, (dimethylamino)methyl, isopropylaminomethyl, cyclobutylaminomethyl, (5-methyl-isoxazol-3-yl)methoxy, (3,5-dimethylisoxazol-4-yl)methoxy, N-methyl-N-(3-dimethylaminopropyl)aminocarbonyl, 4-(1-isopropyl-piperazin-4-yl)carbonyl, 2-(pyrrolidin-1-yl)ethylaminocarbonyl, 3-methoxypropylaminocarbonyl, 2-(diethylamino)ethylaminocarbonyl, (2-methoxy-1-methyl)ethylaminocarbonyl, (tetrahydrofuran-2-yl)methylaminocarbonyl, 2-methoxyethylaminocarbonyl, 2-cyanoethylaminocarbonyl, (N-methyl-N-cyclohexyl)aminocarbonyl or 4-methyl-piperidin-1-ylcarbonyl.

Still more preferably R^1 is (tetrahydropyran-4-yl)-aminocarbonyl, (pyrolidin-1-yl)methyl, (dimethylamino)methyl, (morpholin-4-yl)methyl, morpholin-4-yl, 4-ethylpiperazin-1-yl or aminocarbonylmethyloxy.

Preferably R^2 is hydrogen, C_{1-6}alkyl, chloro or fluoro. More preferably R^2 is hydrogen, methyl, chloro or fluoro. More preferably still, R^2 is methyl.

Preferably R^3 is hydrogen or fluoro.

Preferably, when X is N, R^2 is methyl. More preferably when X is N and R^2 is methyl, R^3 is H.

It will be appreciated that the present invention is intended to include compounds having any combination of the preferred groups listed hereinbefore.

Preferably
either A is S and B is N, or A is N and B is S;
X is N;
R^1 is $-NR^5R^6$, $-(CH_2)_nNR^5R^6$, $-O(CH_2)_n$-Het (wherein Het is preferably imidazolyl or oxazolyl), $-O(CH_2)_nNR^5R^6$, $-CONR^5R^6$, $-SO_2R^7$ or $-O(CH_2)_nCONR^5R^6$;
R^2 is hydrogen, methyl, chloro or fluoro;
R^3 is hydrogen or halo;
R^4 is $-NH_2$;
where
R^5 and R^6 are independently selected from hydrogen; Het (preferably tetrahydropyranyl); C_{3-6}cycloalkyl optionally substituted by C_{1-6}alkyl; or by C_{1-6}alkyl optionally substituted by Het (preferably furyl), alkoxy, cyano or $-NR^aR^b$ (where R^a and R^b which may the same or different are hydrogen or C_{1-6}alkyl, or R^a and R^b together with the nitrogen atom to which they are attached may form a 4, 5 or 6-membered saturated ring); or R^5 and R^6 together with the atom to which they are attached form a morpholine, piperidine, pyrrolidine or piperazine ring, each of which may be substituted by halo (such as fluoro, chloro, bromo), cyano, $-CF_3$, hydroxy, $-OCF_3$, C_{1-4}alkyl or C_{1-4}alkoxy;
R^7 is hydrogen or C_{1-6}alkyl;

Het is a 5 or 6-membered C-linked heterocyclyl group which may be saturated, unsaturated or aromatic, which may contain one or more heteroatoms selected from N, S or O and which may be substituted by C_{1-6}alkyl; and

n is 1-4.

According to a second aspect, the invention provides a compound as defined in the first aspect with the proviso that when A is S; B is N; X is N; R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, cyano, perfluoroC_{1-6}alkyl or perfluoroC_{1-6}alkoxy; R^2 is hydrogen, C_{1-6}alkyl, halo, cyano or perfluoroC_{1-6}alkyl; and R^3 is hydrogen or halo; then R^4 is not NH_2.

Compounds of formula (I) which are of special interest as agents useful in the treatment or prophylaxis of disorders characterised by the overexpression of TGF-β are selected from the list:

5-{2-[4-(4-ethylpiperazin-1-yl)phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine (Example 3);

5-{2-[4-(morpholin-4-yl)phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine (Example 4);

5-{2-[4-(aminocarbonylmethyloxy)-phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine (Example 10);

5-{2-[4-(2-(pyrrolidin-1-yl)-ethoxy)-phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine (Example 11);

4-[2-(4-((tetrahydropyran-4-yl)-aminocarbonyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine (Example 16);

4-[2-(4-(morpholin-4-yl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine (Example 20);

4-[2-(4-(aminocarbonylmethyloxy)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine (Example 22);

4-[2-(4-((pyrrolidin-1-yl)methyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine (Example 24);

4-[2-(4-((dimethylamino)methyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine (Example 25); and

4-[2-(4-((tetrahydropyran-4-yl)aminocarbonyl)phenyl)pyridin-4-yl]-5-[pyridin-2-yl]-1,3-thiazol-2-amine (Example 26);

and pharmaceutically acceptable salts, solvates and derivatives thereof.

For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

As used herein the term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, solvate, ester or amide, or salt or solvate of such ester or amide, of the compound of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) the a compound of formula (I) or an active metabolite or residue thereof, e.g., a prodrug. Preferred pharmaceutically acceptable derivatives according to the invention are any pharmaceutically acceptable salts, solvates or prodrugs.

Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid salts, for example sodium, potassium, calcium, magnesium and tetraalkylammonium and the like, or mono- or di- basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like. Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Hereinafter, compounds, their pharmaceutically acceptable salts, their solvates and polymorphs, defined in any aspect of the invention (except intermediate compounds in chemical processes) are referred to as "compounds of the invention".

The compounds of the invention may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present invention.

Compounds of the invention may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

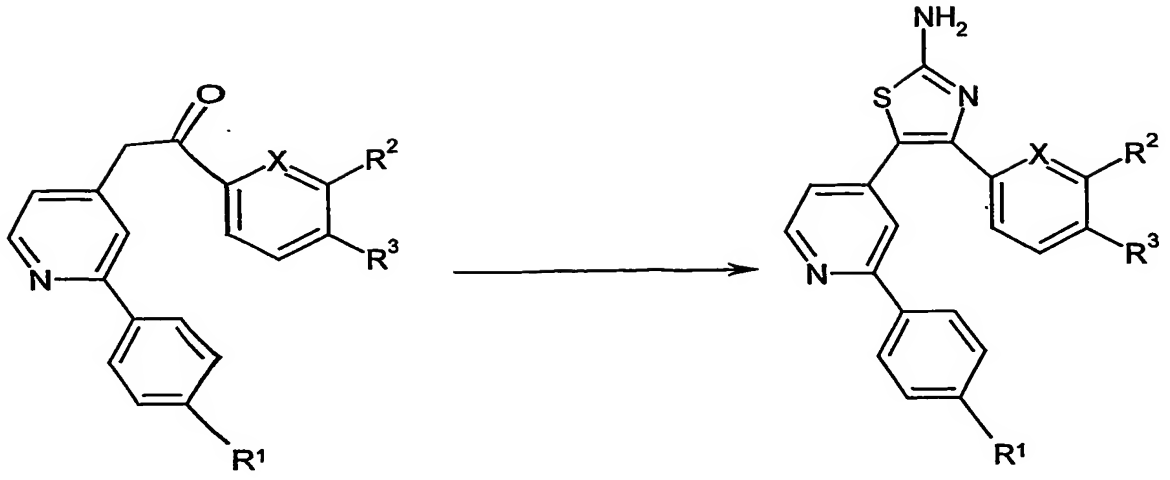
Since the compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention.

Compounds of the invention may be prepared, in known manner in a variety of ways. In the following reaction schemes and hereafter, unless otherwise stated R^1 to R^7, X and n are as defined in the first aspect. These processes form further aspects of the invention.

Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV) etc. Subsets of these general formulae are defined as (Ia), (Ib), (Ic) etc .... (IVa), (IVb), (IVc) etc.

Compounds of formula (Ia), i.e. compounds of general formula (I) where A is S, B is N and R^4 is NH_2, may be prepared by reacting compounds of formula (II) with a suitable polymer-supported bromine reagent, such as polymer-supported pyridinium perbromide, followed by treatment with thiourea in a suitable solvent such as ethanol, preferably at elevated temperatures (see reaction scheme 1).

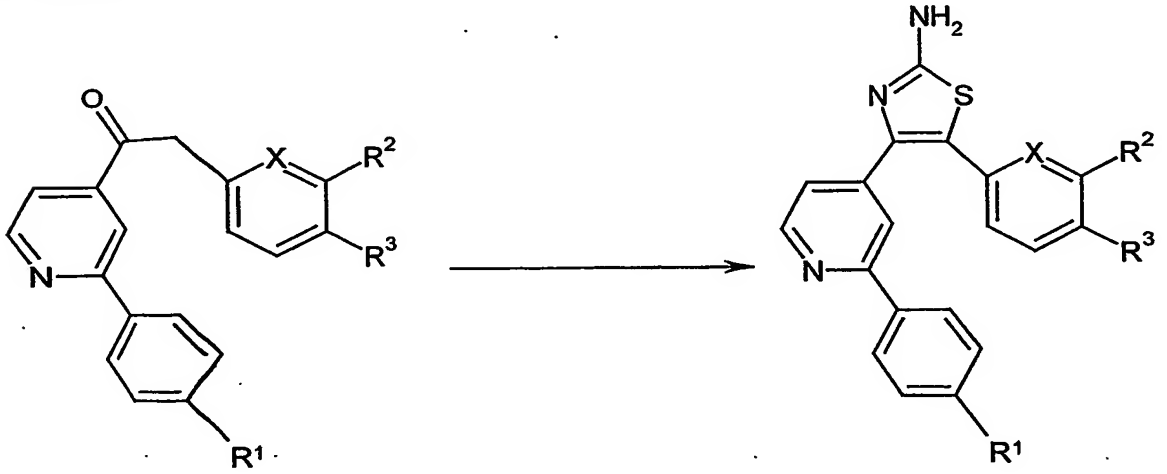
Scheme 1



(II) (Ia)

Compounds of formula (Ib), i.e. compounds of general formula (I) where A is N, B is S and R^4 is NH_2, may be prepared by reacting compounds of formula (III) under analogous conditions to reaction scheme 1 (see reaction scheme 2).

Scheme 2

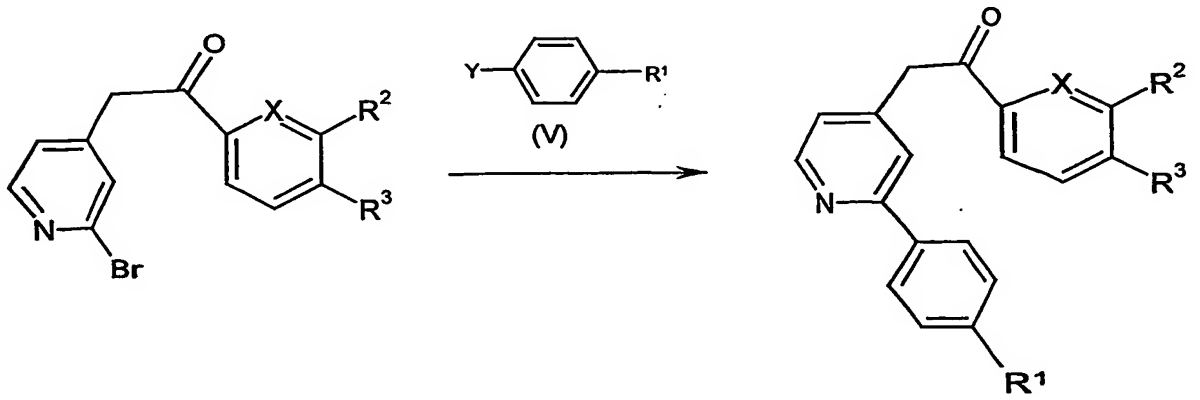


(III) (Ib)

Compounds of formula (II) may be prepared by reacting compounds of formula (IV) with compounds of formula (V) where Y is a boron containing moiety such as $-B(OH)_2$ or 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl according to reaction scheme 3. Preferred conditions comprise reaction with a suitable catalyst such as

tetrakis(triphenylphosphine) palladium (0), in the presence of a suitable base such as sodium carbonate in a suitable solvent such as DME at elevated temperature.

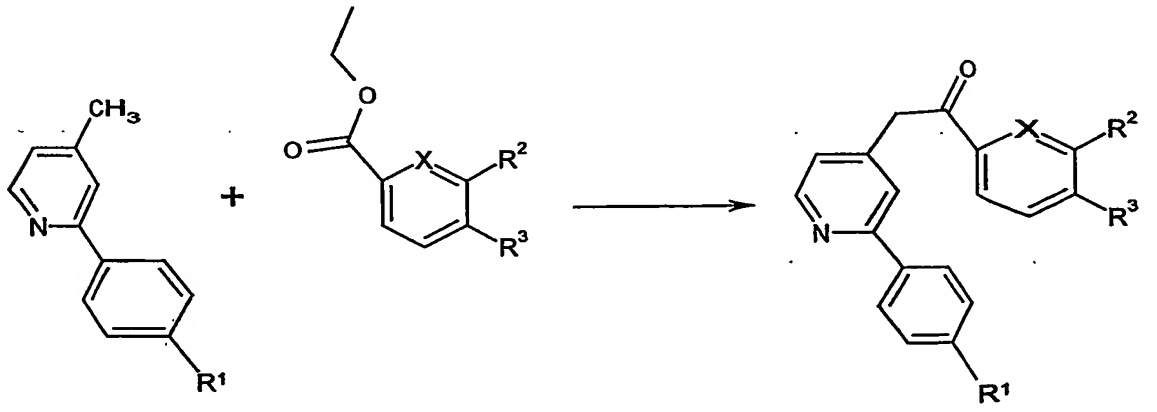
Scheme 3



(IV) (II)

Alternatively compounds of formula (II) may be prepared by reacting compounds of formula (VI) with compounds of formula (VII) according to reaction scheme 4. Preferred reaction conditions comprise reacting (VI) with sodium bis-(trimethylsilyl)amide in a suitable solvent such as tetrahydrofuran at low temperature, preferably -78°C.

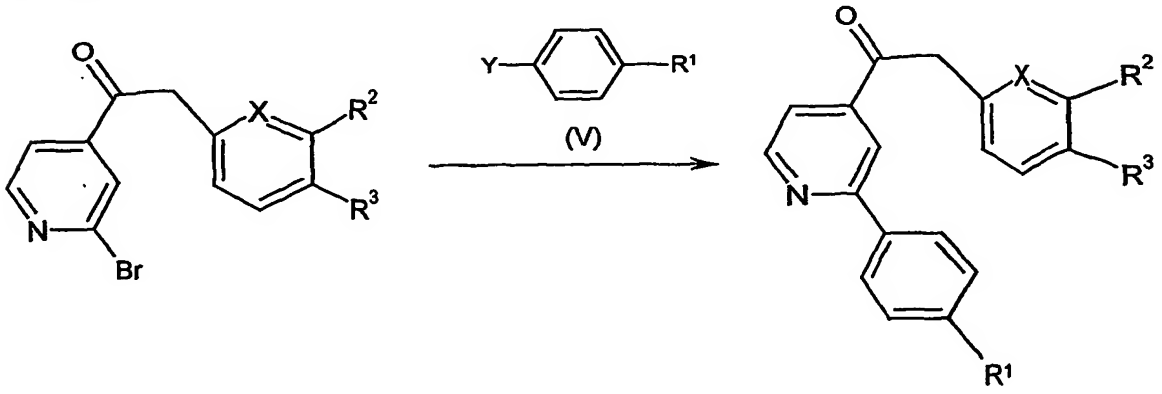
Scheme 4



(VI) (VII) (II)

Compounds of formula (III) may be prepared according to reaction scheme 5 by reacting compounds of formula (VIII) with compounds of formula (V) (where Y is as defined for reaction scheme 3) using analogous reaction conditions to those of reaction scheme 3.

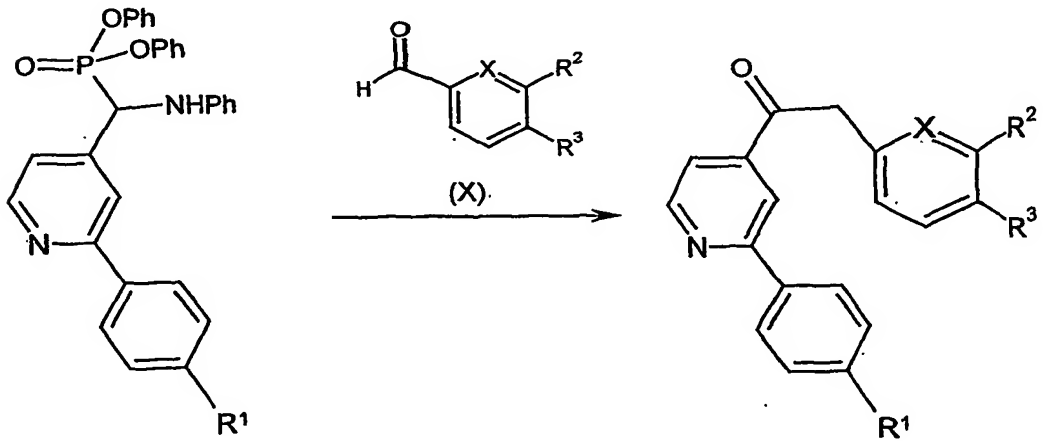
Scheme 5



(VIII) (III)

Alternatively compounds of formula (III) may be prepared according to reaction scheme 6 by reacting compounds of formula (IX) with compounds of formula (X) in the presence of a suitable base such as cesium carbonate in a suitable solvent such as tetrahydrofuran and isopropanol at room temperature.

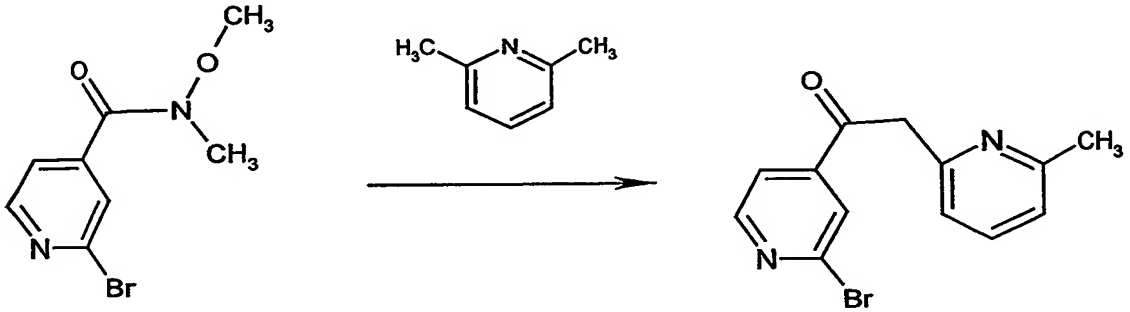
Scheme 6



(IX) (III)

Compounds of formula (VIIIa), i.e. compounds of general formula (VIII) (see scheme 5) where X is N, R^2 is methyl and R^3 is hydrogen, may be prepared according to reaction scheme 7. Preferred conditions comprise reacting 2,6-lutidine with a strong base such as n-butyllithium or sodium bis-(trimethylsilyl) amide at low temperature, followed by addition of 2-bromo-N-methoxy-N-methyl-4-pyridinecarboxamide (see preparation of Intermediate 36 hereinafter)

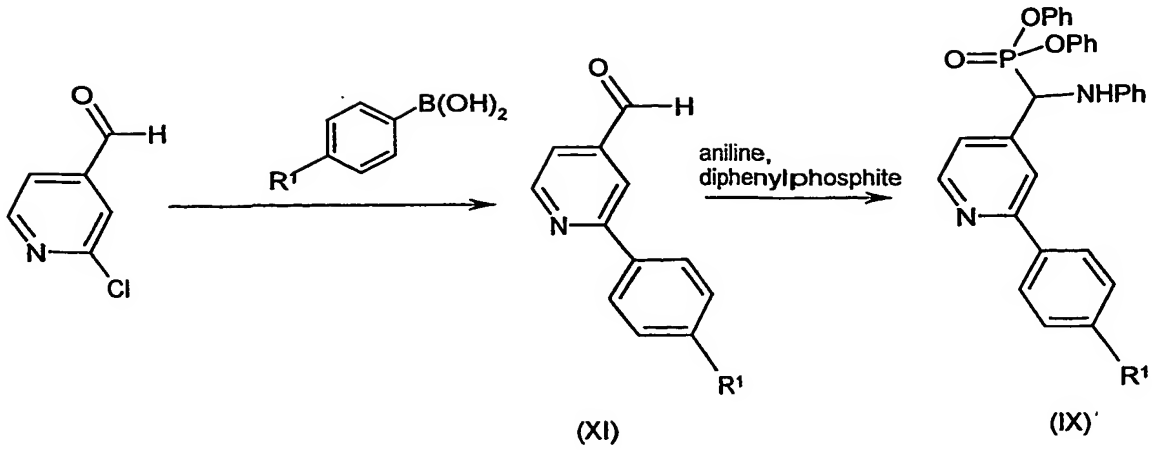
Scheme 7



(VIIIa)

Compounds of formula (IX) may be prepared in two steps according to reaction scheme 8. Preferred reaction conditions for the first step are analogous to those described for reaction scheme 3. Preferred reaction conditions for the second step comprise reacting compounds of formula (XI) with aniline and diphenylphosphite in a suitable solvent such as isopropanol at room temperature.

Scheme 8

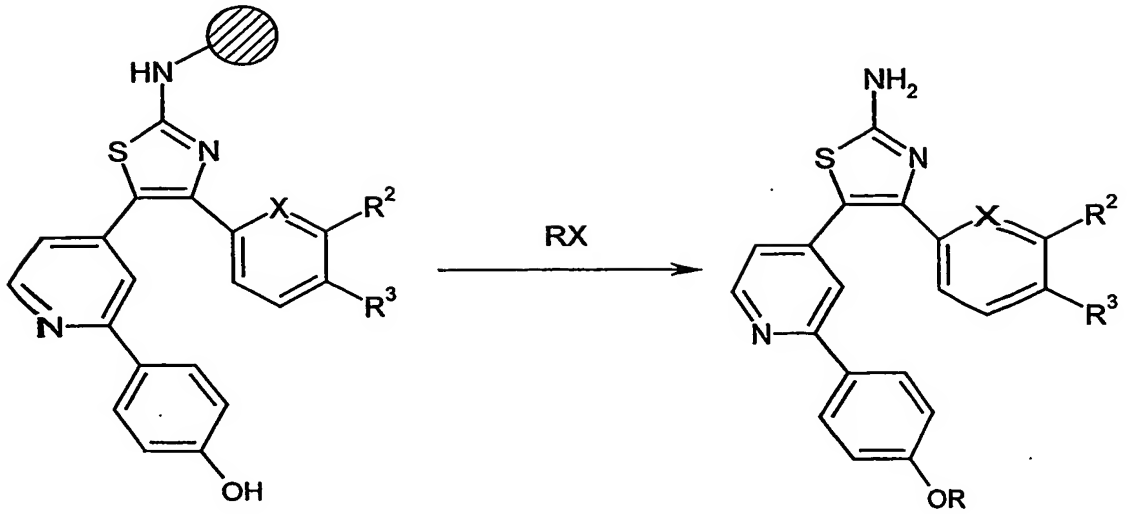


(XI) (IX)

Compounds of general formula (I) may also be prepared using solid supported chemistry.

Compounds of formula (Ic), i.e. compounds of general formula (I) where A is S, B is N, R^1 is –OR (where R is for example $-(CH_2)_n$-Het or $-CH_2CONR^5R^6$) and R^4 is NH_2, may be prepared from solid supported compounds of formula (XII) by reaction with RX (where X is a suitable leaving group such as chlorine) followed by cleavage under acidic conditions from the solid support, according to reaction scheme 9. Preferred conditions comprise treating (XII) with RX under basic conditions such as potassium carbonate in a suitable solvent such as DMSO at elevated temperature. Preferred cleavage conditions are trifluoroacetic acid in a suitable solvent such as dichloromethane at room temperature.

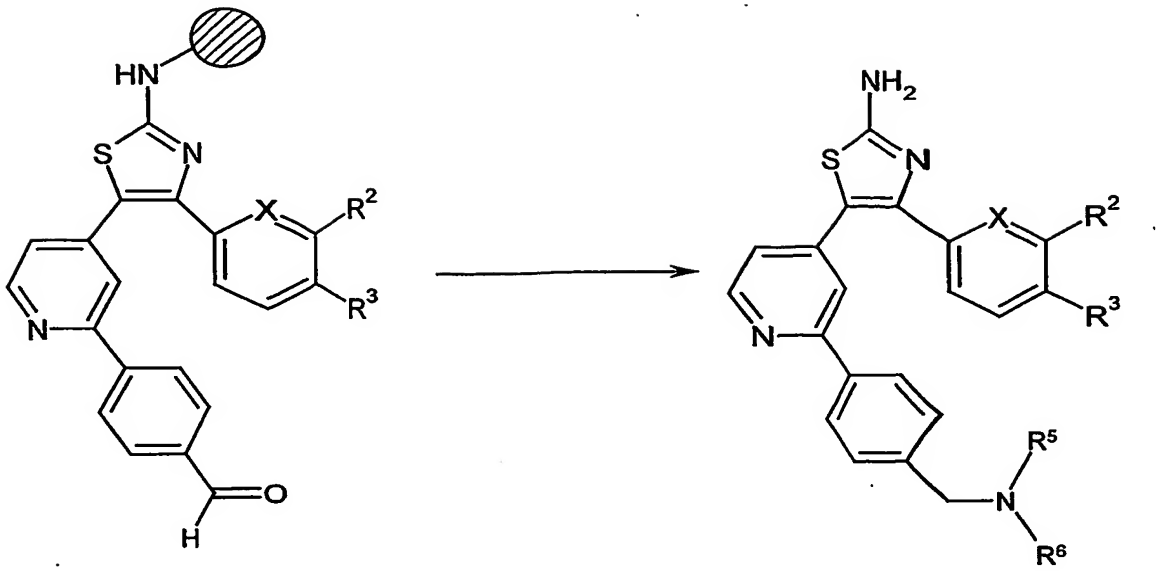
Scheme 9



(XII) (Ic)

Compounds of formula (Id), i.e. compounds of general formula (I) where A is S, B is N, R^1 is $-CH_2NR^5R^6$ and R^4 is NH_2, may be prepared from solid supported compounds of formula (XIII) according to reaction scheme 10. Preferred reaction conditions comprise treating (XIII) with HNR^5R^6 in trimethylorthoformate and addition of a reducing agent, such as sodium cyanoborohydride in acetic acid at elevated temperature. Cleavage from the solid support using trifluoroacetic acid in dichloromethane gives compounds of formula (Id).

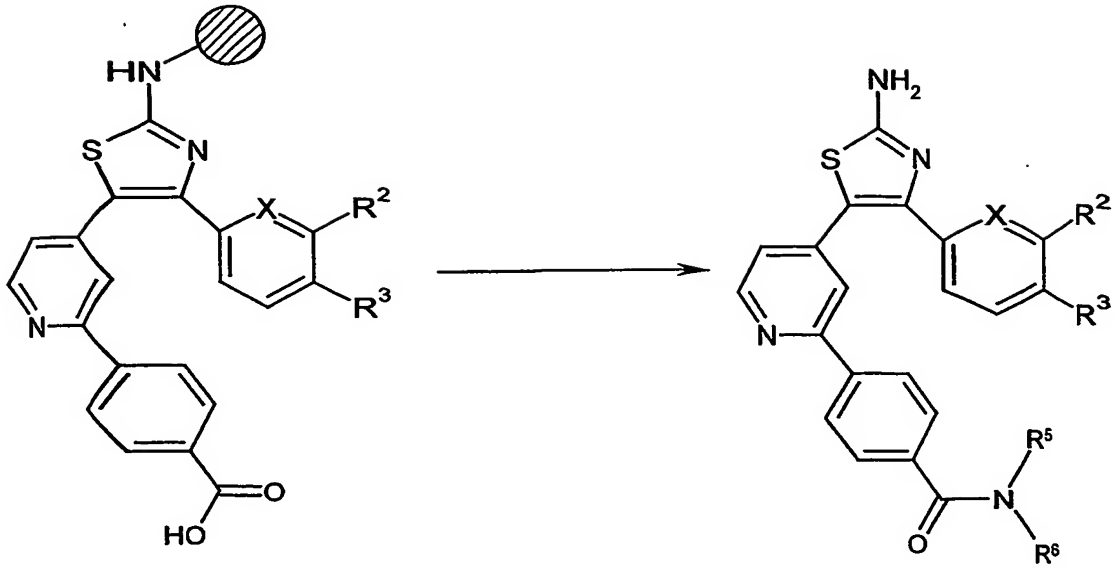
Scheme 10



(XIII) (Id)

Compounds of formula (Ie), i.e. compounds of general formula (I) where A is S, B is N, R^1 is $-C(O)NR^5R^6$ and R^4 is NH_2, may be prepared from solid supported compounds of formula (XIV) according to reaction scheme 11. Preferred reaction conditions comprise treating (XIV) with HNR^5R^6, hydroxybenzotriazole and diisopropylcarbodiimide. Cleavage from the solid support using trifluoroacetic acid in dichloromethane gives compounds of formula (Ie).

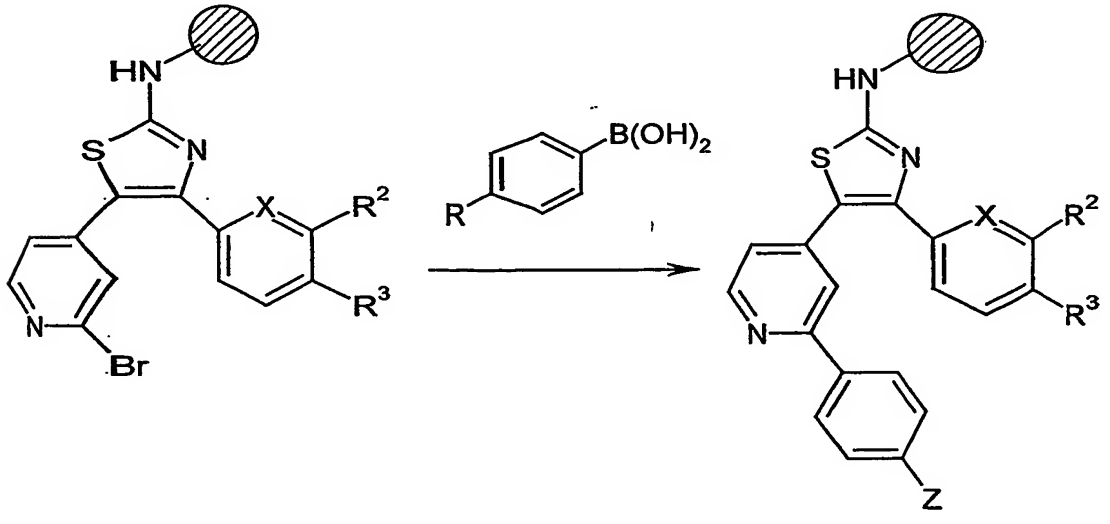
Scheme 11



(XIV) (Ie)

Compounds of formula (XII), (XIII) and (XIV) may be prepared according to reaction scheme 12 from compounds of formula (XV) and the appropriate arylboronic acid (XVI), where Z is –OH, -CHO or $-CO_2H$ respectively.

Scheme 12

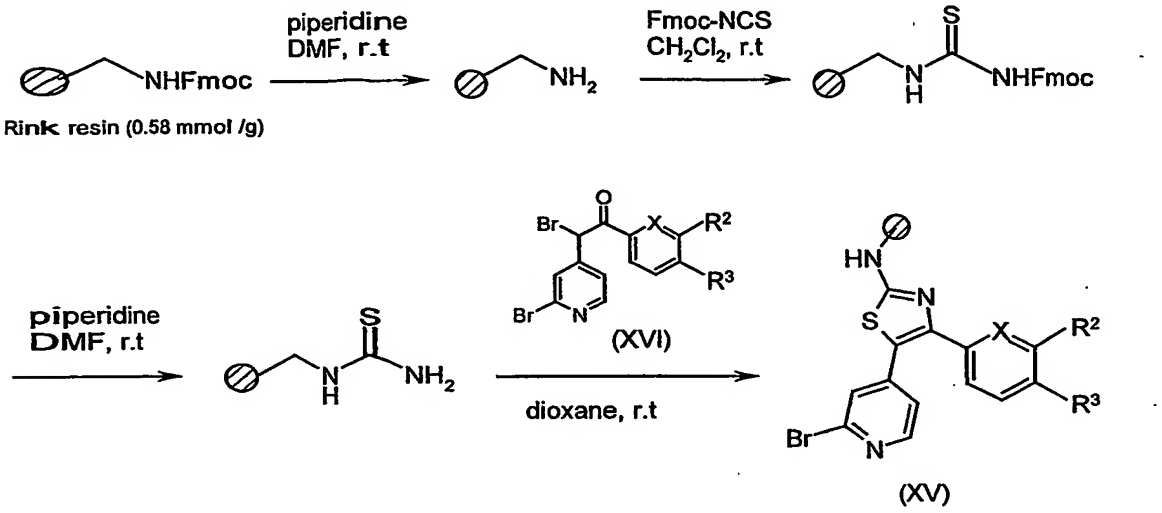


(XV) (XII, XIII, XIV)

Compounds of formula (XV) may be prepared by solid phase synthesis according to reaction scheme 13. Compounds of formula (XVI) may be prepared by treating compounds of formula (IV) (see scheme 3) with a suitable polymer-supported

bromine reagent, such as polymer-supported pyridinium perbromide. Treatment of a resin-bound thiourea with a dioxane solution of compounds of formula (XVI) gives compounds of formula (XV) using general conditions described in the literature (see Kearney P.C., J. Org. Chem., (1998), 63, 196).

Scheme 13



Further details for the preparation of compounds of formula (I) are found in the examples.

The compounds of the invention may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds. Libraries of compounds of the invention may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect there is provided a compound library comprising at least 2 compounds of the invention.

Activation of the TGF-β1 axis and expansion of extracellular matrix are early and persistent contributors to the development and progression of chronic renal disease and vascular disease. Border W.A., *et al*, *N. Engl. J. Med.*, 1994; 331(19), 1286-92. Further, TGF-β1 plays a role in the formation of fibronectin and plasminogen activator inhibitor-1, components of sclerotic deposits, through the action of smad3

phosphorylation by the TGF-β1 receptor ALK5. Zhang Y., *et al*, *Nature*, 1998; 394(6696), 909-13; Usui T., *et al*, *Invest. Ophthalmol. Vis. Sci.*, 1998; 39(11), 1981-9.

Progressive fibrosis in the kidney and cardiovascular system is a major cause of suffering and death and an important contributor to the cost of health care. TGF-β1 has been implicated in many renal fibrotic disorders. Border W.A., *et al*, *N. Engl. J. Med.*, 1994; 331(19), 1286-92. TGF-β1 is elevated in acute and chronic glomerulonephritis Yoshioka K., *et al*, *Lab. Invest.*, 1993; 68(2), 154-63, diabetic nephropathy Yamamoto, T., *et al*, 1993, *PNAS* 90, 1814-1818., allograft rejection, HIV nephropathy and angiotensin-induced nephropathy Border W.A., *et al*, *N. Engl. J. Med.*, 1994; 331(19), 1286-92. In these diseases the levels of TGF-β1 expression coincide with the production of extracellular matrix. Three lines of evidence suggest a causal relationship between TGF-β1 and the production of matrix. First, normal glomeruli, mesangial cells and non-renal cells can be induced to produce extracellular-matrix protein and inhibit protease activity by exogenous TGF-β1 in vitro. Second, neutralizing anti-bodies against TGF-β1 can prevent the accumulation of extracellular matrix in nephritic rats. Third, TGF-β1 transgenic mice or in vivo transfection of the TGF-β1 gene into normal rat kidneys resulted in the rapid development of glomerulosclerosis. Kopp J.B., *et al*, *Lab. Invest.*, 1996; 74(6), 991-1003. Thus, inhibition of TGF-β1 activity is indicated as a therapeutic intervention in chronic renal disease.

TGF-β1 and its receptors are increased in injured blood vessels and are indicated in neointima formation following balloon angioplasty Saltis J., *et al*, *Clin. Exp. Pharmacol. Physiol.*, 1996; 23(3), 193-200. In addition TGF-β1 is a potent stimulator of smooth muscle cell ("SMC") migration in vitro and migration of SMC in the arterial wall is a contributing factor in the pathogenesis of atherosclerosis and restenosis. Moreover, in multivariate analysis of the endothelial cell products against total cholesterol, TGF-β receptor ALK5 correlated with total cholesterol ($P < 0.001$) Blann A.D., *et al*, *Atherosclerosis*, 1996; 120(1-2), 221-6. Furthermore, SMC derived from human atherosclerotic lesions have an increased ALK5/TGF-β type II receptor ratio. Because TGF-β1 is over-expressed in fibroproliferative vascular lesions, receptor-variant cells would be allowed to grow in a slow, but uncontrolled fashion, while overproducing extracellular matrix components McCaffrey T.A., *et al*, Jr., *J. Clin. Invest.*, 1995; 96(6), 2667-75. TGF-β1 was immunolocalized to non-foamy

macrophages in atherosclerotic lesions where active matrix synthesis occurs, suggesting that non-foamy macrophages may participate in modulating matrix gene expression in atherosclerotic remodelling via a TGF-β-dependent mechanism. Therefore, inhibiting the action of TGF-β1 on ALK5 is also indicated in atherosclerosis and restenosis.

TGF-β is also indicated in wound repair. Neutralizing antibodies to TGF-β1 have been used in a number of models to illustrate that inhibition of TGF-β1 signalling is beneficial in restoring function after injury by limiting excessive scar formation during the healing process. For example, neutralizing antibodies to TGF-β1 and TGF-β2 reduced scar formation and improved the cytoarchitecture of the neodermis by reducing the number of monocytes and macrophages as well as decreasing dermal fibronectin and collagen deposition in rats Shah M., *J. Cell. Sci.*, 1995, 108, 985-1002. Moreover, TGF-β antibodies also improve healing of corneal wounds in rabbits Moller-Pedersen T., *Curr. Eye Res.*, 1998, 17, 736-747, and accelerate wound healing of gastric ulcers in the rat; Ernst H., *Gut*, 1996, 39, 172-175. These data strongly suggest that limiting the activity of TGF-β would be beneficial in many tissues and suggest that any disease with chronic elevation of TGF-β would benefit by inhibiting smad2 and smad3 signalling pathways.

TGF-β is also implicated in peritoneal adhesions Saed G.M., *et al*, *Wound Repair Regeneration*, 1999 Nov-Dec, 7(6), 504-510. Therefore, inhibitors of ALK5 would be beneficial in preventing peritoneal and sub-dermal fibrotic adhesions following surgical procedures.

TGF-β is also implicated in photoaging of the skin (see Fisher GJ. Kang SW. Varani J. Bata-Csorgo Z. Wan YS. Data S. Voorhees JJ. , Mechanisms of photoaging and chronological skin ageing, *Archives of Dermatology*, 138(11):1462-1470, 2002 Nov. and Schwartz E. Sapadin AN. Kligman LH. "Ultraviolet B radiation increases steady state mRNA levels for cytokines and integrins in hairless mouse skin- modulation by topical tretinoin", Archives if Dermatological Research, 290(3):137-144, 1998 Mar.)

Therefore according to a further aspect, the invention provides the use of a compound defined in the first aspect in the preparation of a medicament for treating or preventing a disease or condition mediated by ALK-5 inhibition.

Preferably the disease or condition mediated by ALK-5 inhibition is selected from the list: chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers (including diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers), ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to kidney fibrosis, lung fibrosis and liver fibrosis, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis, primary biliary cirrhosis, restenosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis, keloids, cancer, abnormal bone function, inflammatory disorders, scarring and photaging of the skin.

More preferably the disease or condition mediated by ALK-5 inhibition is fibrosis. Preferably kidney fibrosis.

It will be appreciated that references herein to treatment extend to prophylaxis as well as the treatment of established conditions.

Compounds of the invention may be administered in combination with other therapeutic agents, for example antiviral agents for liver diseases, or in combination with ACE inhibitors or angiotensin II receptor antagonists for kidney diseases.

The compounds of the invention may be administered in conventional dosage forms prepared by combining a compound of the invention with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

The compositions may be formulated for administration by any route. The compositions may be in the form of tablets, capsules, powders, granules, lozenges,

creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilising the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilised powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

It will be recognised by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of the invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

No toxicological effects are indicated when a compound of the invention is administered in the above-mentioned dosage range.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

It will be appreciated that the invention includes the following further aspects. The preferred embodiments described for the first aspect extend these further aspects:

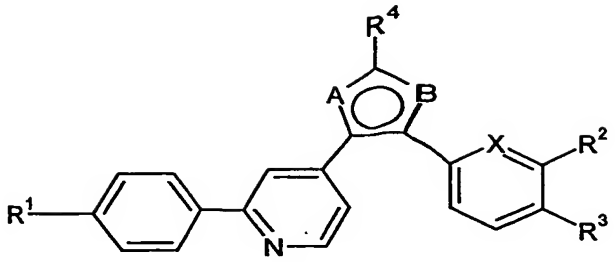
i) a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or diluent;

ii) a compound of the invention for use as a medicament;

iii) a method of treatment or prophylaxis of a disorder selected from chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis, kidney fibrosis, liver fibrosis [for example, hepatitis B virus (HBV), hepatitis C virus (HCV)], alcohol induced hepatitis, retroperitoneal fibrosis, mesenteric fibrosis, haemochromatosis and primary biliary cirrhosis, endometriosis, keloids, restenosis and photoaging of the skin, in mammals, which comprises administration to the mammal in need of such treatment, an effective amount of a compound of the invention; and

iv) a combination of a compound of the invention with an ACE inhibitor or an angiotensin II receptor antagonist.

According to a further aspect, the invention provides a compound of formula (I), a pharmaceutically acceptable salt, solvate or derivative thereof;



(I)

wherein

A is S and B is N;

X is N or CH;

R^1 is selected from H, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo, cyano, perfluoro C_{1-6}alkyl, perfluoroC_{1-6}alkoxy, $-NR^5R^6$, $-(CH_2)_nNR^5R^6$, $-O(CH_2)_nOR^7$, $-O(CH_2)_nNR^5R^6$, $-CONR^5R^6$, $-CO(CH_2)_nNR^5R^6$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NR^5SO_2R^7$ and $-NR^5COR^7$;

R^2 is selected from H, C_{1-6}alkyl, halo, CN or perfluoroC_{1-6}alkyl;

R^3 is selected from H or halo;

R^4 is selected from $-NR^5R^6$;

R^5, R^6 and R^7 are independently selected from H or C_{1-6}alkyl; or R^5 and R^6 together with the atom to which they are attached form a 3, 4, 5, 6 or 7-membered saturated or unsaturated ring which may contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more substituents selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl and C_{1-6} alkoxy; and

n is 1-4;

with the proviso that the compound of formula (I) is not:

5-[2-(4-chlorophenyl)pyridin-4-yl]-4-pyridin-2-yl-1,3-thiazol-2-amine;

5-[2-(4-methoxyphenyl)pyridin-4-yl]-4-pyridin-2-yl-1,3-thiazol-2-amine;

5-[2-(4-fluorophenyl)pyridin-4-yl]-4-pyridin-2-yl-1,3-thiazol-2-amine;

5-[2-(4-ethylphenyl)pyridin-4-yl]-4-pyridin-2-yl-1,3-thiazol-2-amine; or

5-[2-(4-ethoxyphenyl)pyridin-4-yl]-4-pyridin-2-yl-1,3-thiazol-2-amine.

According to a still further aspect, the invention provides a compound of formula (I), a pharmaceutically acceptable salt, solvate or derivative thereof;

wherein

A is S and B is N;

X is N or CH;

R^1 is selected from H, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo, cyano, perfluoro C_{1-6}alkyl, perfluoroC_{1-6}alkoxy, $-NR^5R^6$, $-(CH_2)_nNR^5R^6$, $-O(CH_2)_nOR^7$, $-O(CH_2)_nNR^5R^6$, $-CONR^5R^6$, $-CO(CH_2)_nNR^5R^6$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NR^5SO_2R^7$ and $-NR^5COR^7$;

R^2 is selected from H, C_{1-6}alkyl, halo, CN or perfluoroC_{1-6}alkyl;

R^3 is selected from H or halo;

R^4 is selected from $-NR^5R^6$;

R^5, R^6 and R^7 are independently selected from H or C_{1-6}alkyl; or R^5 and R^6 together with the atom to which they are attached form a 3, 4, 5, 6 or 7-membered saturated or unsaturated ring which may contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more substituents selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl and C_{1-6} alkoxy; and

n is 1-4;

with the proviso that when A is S; B is N; X is N; R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, cyano, perfluoroC_{1-6}alkyl or perfluoroC_{1-6}alkoxy; R^2 is hydrogen, C_{1-6}alkyl, halo, cyano or perfluoroC_{1-6}alkyl; and R^3 is hydrogen or halo; then R^4 is not NH_2.

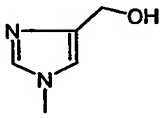
The following non-limiting examples illustrate the present invention.

Abbreviations

Binap	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
CH_2Cl_2	dichloromethane
DMF	dimethylformamide
DME	1,2-Dimethoxyethane
DMSO	dimethylsulfoxide
EDCI	1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
Et_2O	diethyl oxide
EtOH	ethanol
Et_3N	triethylamine
Fmoc-NCS	fluoromethylcarbonyl isothiocyanate
HOBT	hydroxybenzotriazole
MeOH	methanol
NaH	sodium hydride
$NaHCO_3$	sodium hydrogen carbonate

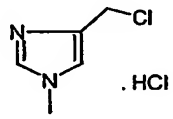
NaHMDS	sodium bis(trimethylsilyl)amide
NH_4Cl	ammonium chloride
Na_2SO_4	sodium sulfate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium (0)
THF	tetrahydrofuran

Intermediate 1: 1-methyl-4-hydroxymethyl-imidazole



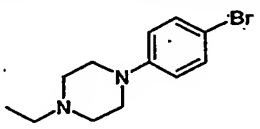
To a suspension of 1-methyl-imidazole-4-carboxylic acid (11.4g, 90 mmol) in THF (500ml) at 0°C, was added dropwise lithium aluminium hydride (solution 1M in THF, 117ml, 117 mmol) and the mixture was stirred at room temperature overnight and then at 50°C for 1 hour. Then water (3 ml) was added followed by Na_2SO_4, and the resulting precipitate was filtered off on a celite pad. The filtrate was concentrated under reduced pressure to afford the title compound as a solid (8g, 78.95%); ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.25 (s, 1H), 6.7 (s, 1H), 5.25 (m, 1H), 4.4 (s, 2H), 3.45 (s, 3H).

Intermediate 2: 1-methyl-4-chloromethyl-imidazole hydrochloride



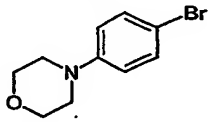
To a solution of intermediate 1 (5g, 44.64 mmol) in CH_2Cl_2 (10 ml) at 0°C was added dropwise thionyl chloride (50 ml) and then the mixture was stirred at room temperature overnight and then under reflux for 3 hours and then concentrated under reduced pressure. The residue was treated with diethyl oxide and the resulting precipitate was filtered and dried. The title compound was obtained as a brown solid (4g, 53.81%); ^1H NMR (300 MHz, d^6-DMSO, ppm) δ: 9.25 (s, 1H), 7.8 (s, 1H), 4.95 (s, 2H), 3.9 (s, 3H).

Intermediate 3: 1-ethyl-4-(4-bromophenyl)-piperazine



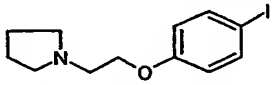
To a solution of 1-ethyl–4-phenyl-piperazine (18g, 95mmol) in ethanol (600ml) cooled in an iced bath, was added dropwise bromine (5.1ml, 99mmol). The mixture was stirred at room temperature for 2 hours and then poured into water. The solution was made basic by addition of a solution of 1N sodium hydroxide. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH (9/1). The titled compound was obtained as a solid (21g, 82.4%); [APCI MS] m/z 270 (MH^+).

Intermediate 4 : 4-bromophenyl-morpholine



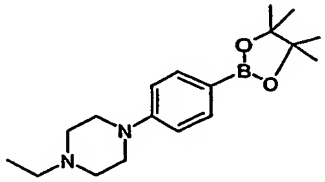
4-Phenyl-morpholine (18g, 110.4mmol) was reacted as described for intermediate 3 to afford, after crystallisation from diisopropyl oxide, the titled compound as a white solid (15g, 56.13%); m.p. 126-128°C.

Intermediate 5 : 4-(2-(pyrrolidin-1-yl)-ethoxy)-iodobenzene



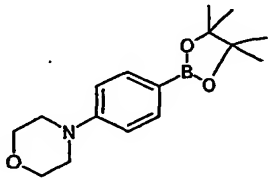
To a solution of 4-iodo–phenol (6g, 27.3mmol) in acetone (200ml) were added cesium carbonate (22.2g, 68.4 mmol) and N-(2-chloroethyl)-pyrrolidine hydrochloride (7g, 41 mmol) and the mixture was heated under reflux during 4 hours and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The titled compound was obtained as a red oil (8g, 92.53%); ^1H NMR (300MHz, $CDCl_3$, ppm) δ: 7.5 (d, 2H), 6.65 (d, 2H), 4 (t, 2H), 2.8 (t, 2H), 2.55 (m, 4H), 1.75 (m, 4H).

Intermediate 6: 1-ethyl–4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-piperazine



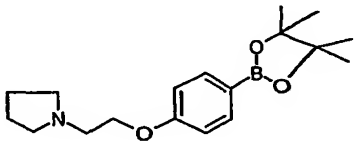
To a solution of intermediate 3 (3g, 11mmol) in dioxane (100ml) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.8ml, 12mmol), dichlorobis(triphenylphosphine)palladium(II) (0.392g, 0.57mmol), triethylamine (4.65ml, 33mmol) and the mixture was heated under reflux for 12 hours and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH (9/1). The titled compound was obtained as a brown oil which crystallised on standing (2g, 55.48%); m.p. 130-134°C.

Intermediate 7: 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-morpholine



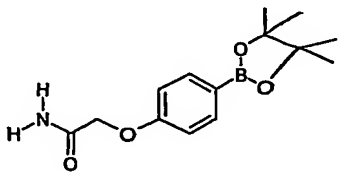
Intermediate 4 (15g, 62mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9.8ml, 68mmol) were reacted as described for intermediate 6 to afford the titled compound as a solid (15g, 83.74%); m.p. 114-116°C.

Intermediate 8: 1-[2-(pyrrolidin-1-yl)-ethoxy]-4-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]-benzene



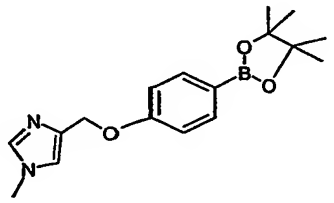
Intermediate 5 (8g, 25.24mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ml, 27.6mmol) were reacted as described for intermediate 6 to afford the titled compound as a solid (8g, 99.99%); m.p. 160-164°C.

Intermediate 9: 1-[aminocarbonylmethyloxy]-4-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]-benzene



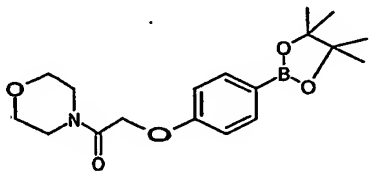
To a solution of 4-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]-phenol (5g, 22.7mmol) in acetone (80ml) were added cesium carbonate (10.37g, 32 mmol) and bromoacetamide (4.39g, 32 mmol) and the mixture was heated at 70°C for 3 hours and then concentrated under reduced pressure. The residue was treated with water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, and concentrated. After trituration with diisopropyl oxide, the title compound was obtained as a solid (4g, 63.54%); m.p. 166-168°C.

Intermediate 10 : 1-[(1-methyl-imidazol-4-yl)-methyloxy]-4-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]-benzene



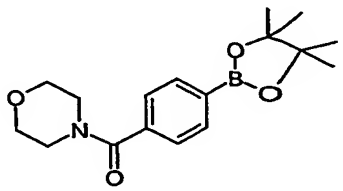
4-[4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl]-phenol (1g, 4.54 mmol) and intermediate 2 (1.88g, 11.4 mmol) were reacted as described for intermediate 9 to afford, after chromatography on silica gel (CH_2Cl_2/MeOH, 95:5), the title compound as a pale yellow oil (0.5g, 35%); ^{1}H NMR (300MHz, $CDCl_3$, ppm) δ: 7.6 (d, 2H), 7.3 (s, 1H), 6.8 (m, 3H), 4.9 (s, 2H), 3.5 (s, 3H), 1.2 (s, 12H).

Intermediate 11: 1-[(morpholin-4-yl)carbonylmethyloxy]-4-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]-benzene



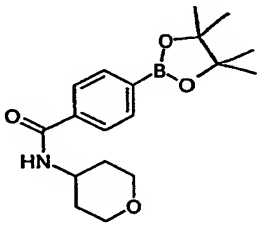
To a solution of 4-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]-phenol (6.6g, 30mmol) in CH_3CN were added potassium carbonate (12.42g, 90 mmol) and N-(chloroacethyl)-morpholine (4.89g, 30 mmol) and the mixture was heated under reflux for 3 hours and then concentrated under reduced pressure. The residue was treated with water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, and concentrated. After trituration with hexane, the title compound was obtained as a grey solid (9.5g, 91%); m.p. 112°C; [APCI MS] m/z 348 (MH+).

Intermediate 12 : N-[(4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl)carbonyl]-morpholine



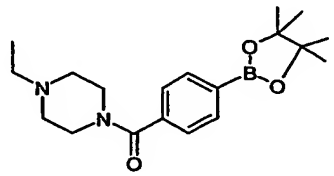
To a solution of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (5g, 20.15 mmol) in CH_2Cl_2/DMF (50ml/5ml) were added morpholine (2.1ml, 24.2mmol), HOBT (3.3g, 24.2mmol), EDCI (4.65g, 24.2mmol) and triethylamine (4.2ml, 30.2mmol) and the reaction mixture was stirred at room temperature for 3 days. Water was added and the product was extracted with CH_2Cl_2, the organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. After trituration with diisopropyl oxide, the title compound was obtained as a white solid (4.21g, 66%); ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.8 (d, 2H), 7.4 (d, 2H), 3.7 (m, 4H), 3.55 (m, 2H), 3.35 (m, 2H), 1.3 (s, 12H).

Intermediate 13: 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-(tetrahydro-pyran-4-yl)-benzamide



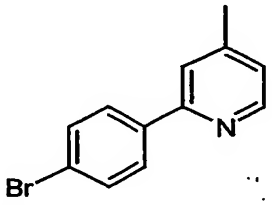
4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (70.16g, 0.28 mol) was treated with $SOCl_2$ (2 vol.) and the reaction mixture was stirred to reflux for 2 hours. After evaporation, the residue was diluted in toluene and poured into a solution at 10°C of tetrahydro-pyran-4-ylamine (34.34g, 0.339) and triethylamine (79 mL, 0.57 mol) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 2 days and water (490 mL) was added to give a precipitate which was filtered off and washed with ethyl acetate. After purification by flash chromatography using CH_2Cl_2/MeOH (95:5). The title compound was obtained as a solid (17.02g, 18%); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.85 (d, 2H), 7.72 (d, 2H), 5.98 (m, 1H), 4.20 (s, 1H), 3.99 (m, 2H), 3.35 (t, 2H), 2.01 (d, 2H), 1.57 (m, 2H), 1.35 (s, 12H).

Intermediate 14: 1-ethyl-4-[(4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl)carbonyl]-piperazine



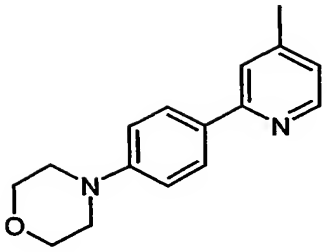
4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (8.24g, 33.22 mmol) and N-ethylpiperazine (5.1ml, 39.87mmol) were reacted as described for intermediate 12 to afford, after chromatography on silica gel (CH_2Cl_2/MeOH, 95:5), the title compound as a pale yellow oil which crystallised (9.64g, 84%); [APCI MS] m/z 345 (MH^+).

Intermediate 15: 2-(4-bromophenyl)-4-methyl-pyridine



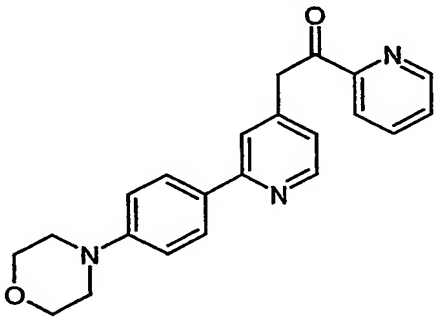
2-Bromo-4-methylpyridine (10 g, 58.14 mmol) was dissolved in toluene (100 ml) and tetrakis(triphenylphosphine)palladium(0) (5 mol%, 3.36 g) added under N_2 and degassed. Aqueous sodium carbonate (2M, 2 eq) was added slowly and stirred for 10min. A solution of 4-bromophenylboronic acid (Lancaster, 14 g, 1.2 eq) in ethanol (20 ml) was added dropwise and the mixture was heated under reflux overnight and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel (CH_2Cl_2/cyclohexane 6:4 then 8:2 then CH_2Cl_2) . After crystallisation from pentane, the title compound was obtained as white crystals (6.3g, 43.7%); ^1H NMR (300MHz, $CDCl_3$, ppm) δ: 8.5 (d, 1H), 7.83 (d, 2H), 7.56 (d, 2H), 7.5 (s, 1H), 7.05 (m, 1H), 2.4 (s, 3H).

Intermediate 16: 2-[4-(morpholin-4-yl)phenyl]-4-methyl-pyridine



To a solution of intermediate 15 (2.66 g, 10.72 mmol) in toluene (50 ml) was added morpholine (1.12 ml, 1.2 eq, 12.9 mmol), $Pd_2(dba)_3$ (0.49g, 0.05 eq, 0.53 mmol), binap (1g, 0.15 eq, 1.6 mmol) and potassium tert-butoxide (1.44g, 1.4 eq, 15 mmol) and the mixture was heated under reflux for 2 h and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH gradient from 99:1 to 95:5) .The title compound was obtained as a yellow solid (2.6g, 95.43%); ^1H NMR (300MHz, $CDCl_3$, ppm) δ: 8.5 (d, 1H), 7.95 (d, 2H), 7.5 (s, 1H), 7 (m, 3H), 3.9 (m, 4H), 3.3 (m, 4H), 2.4 (s, 3H).

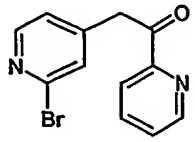
Intermediate 17: 2-[2-(4-(morpholin-4-yl)phenyl)-pyridin-4-yl]-1-pyridin-2-yl-ethanone



To a solution of Intermediate 16 (2.6 g, 10.24 mmol) in dry THF (100 ml) under argon, was added dropwise a solution of sodium bis(trimethylsilyl)amide (1M in THF, 22.52 ml, 2.2 eq, 22.53 mmol). The solution was stirred at room temperature for 0.5h, then a solution of ethyl picolinate (1.66 ml, 1.2 eq, 12.3 mmol) in dry THF (20 ml) was added dropwise and the reaction mixture stirred at room temperature for 4 hours. The solvent was evaporated under reduced pressure and the solid precipitated with diisopropyl oxide. The brown solid was then taken up in saturated NH_4Cl solution and the aqueous phase extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to leave a residue which was purified by chromatography on silicagel (CH_2Cl_2 then CH_2Cl_2/MeOH gradient from 99:1 to 97:3). The title compound was obtained as an orange oil (1.42 g, 38.64%); ^1H NMR (300MHz, $CDCl_3$, ppm) δ: 8.7 (d, 1H), 8.55 (d,

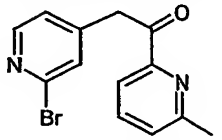
1H), 8.05 (d, 1H), 7.9 (d, 2H), 7.8 (m, 1H), 7.5 (m, 1H), 7.15 (m, 1H), 6.95 (m, 3H), 4.55 (s, 2H), 3.85 (m, 4H), 3.2 (m, 4H).

Intermediate 18: 2-[2-bromo-pyridin-4-yl]-1-pyridin-2-yl-ethanone



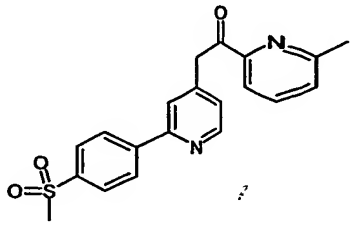
To a solution of 2-bromo-4-methyl-pyridine (27 g) in dry THF (270 ml) was added ethyl picolinate (28.5 g). The resulting mixture was cooled to -78°C under argon and a solution of sodium bis(trimethylsilyl)amide (1M in THF, 345 ml) was added dropwise at -78°C. The resulting reaction mixture was allowed to reach room temperature and subsequently stirred overnight. The solvent was evaporated under reduced pressure and the solid residue triturated with Et_2O, filtered and washed with Et_2O. The solid was then diluted with saturated NH_4Cl solution and the aqueous phase extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The resulting orange powder was washed with pentane to give the title compound as a yellow solid (33.97 g); m.p. 111.2°C.

Intermediate 19 : 2-[2-Bromo-pyridin-4-yl]-1-(6-methyl-pyridin-2-yl)-ethanone



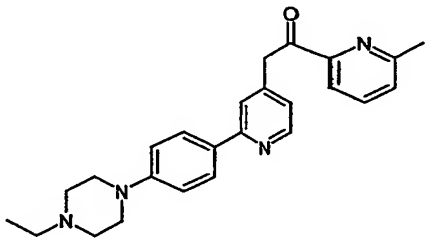
To a solution of 2-bromo-4-methyl-pyridine (5 g, 29mmol) in dry THF (70 ml), a solution of sodium bis(trimethylsilyl)amide 2M in THF (32 ml, 2.2eq) was added dropwise at –30°C under nitrogen. The mixture was stirred at –30°C for 1h, then 6-methylpicolinic acid methyl ester (4.82 g, 32.3mmol, 1.1eq) was added. The reaction mixture was stirred at room temperature overnight. Et_2O was added and the precipitated solid filtered and washed with Et_2O. The solid was then treated with saturated NH_4Cl solution and the aqueous phase extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The resulting orange powder was washed with pentane to give the title compound as a yellow solid (5.84 g, 70%); [APCI MS] m/z : 292 (MH^+).

Intermediate 20: 2-[2-(4-(methanesulfonyl)phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



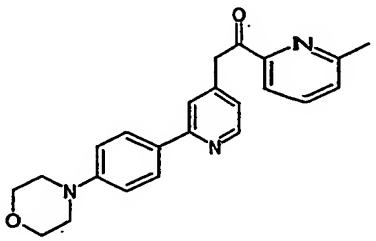
To a solution of intermediate 19 (2g, 6.87mmol) in DME (80ml) was added 4-(methanesulfonyl)-phenyl boronic acid (2.1g, 10.31mmol), tetrakis(triphenylphosphine)palladium(0) (0.4g, 0.35mmol), Na_2CO_3 (solution 2M, 22ml) and the mixture was heated under reflux overnight and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH (95:5). The title compound was obtained as a yellow oil (1.1g, 43.73%); [APCI MS] m/z: 367 (MH^+).

Intermediate 21: 2-[2-(4-(4-ethylpiperazin-1-yl)-phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



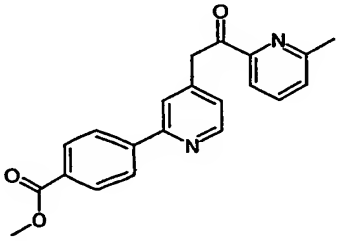
A mixture of intermediate 19 (0.6g, 2 mmol) and intermediate 6 (0.76g, 2.4mmol) were reacted as described for intermediate 20 to afford the title compound as a yellow solid (0.5g, 62.8%); [APCI MS] m/z 387 (MH^+).

Intermediate 22: 2-[2-(4-(morpholin-4-yl)-phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



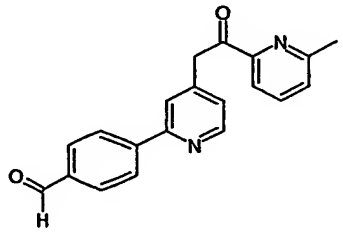
A mixture of intermediate 19 (1.4g, 4.8 mmol) and intermediate 7 (1.8g, 6.2mmol) were reacted as described for intermediate 20 to afford the title compound as a yellow oil (1.2g, 66.9%); [APCI MS] m/z 374 (MH^+).

Intermediate 23 : 2-[2-(4-(methoxycarbonyl)-phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



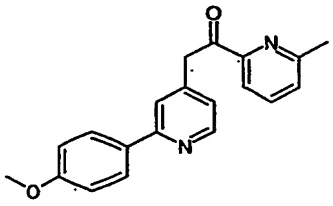
A mixture of intermediate 19 (2g, 6.9 mmol) and 4-(methoxycarbonyl)-phenylboronic acid (1.9g, 10.4mmol) were reacted as described for intermediate 20 to afford the title compound as an orange oil which crystallised on standing (1.2g, 50.5%); [APCI MS] m/z 347 (MH^+).

Intermediate 24: 2-[2-(4-(formyl)-phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



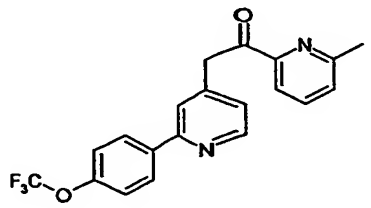
A mixture of intermediate 19 (1g, 3.4 mmol) and 4-(formyl)-phenylboronic acid (0.78g, 5.16mmol) were reacted as described for intermediate 20 to afford the title compound as an orange oil (1g, 92.1%); [APCI MS] m/z 317 (MH^+).

Intermediate 25 : 2-[2-(4-methoxyphenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



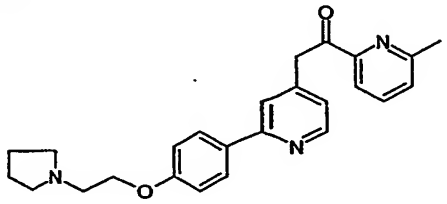
A mixture of intermediate 19 (1g, 3.4 mmol) and 4-methoxyphenylboronic acid (0.63g, 4mmol) were reacted as described for intermediate 20 to afford the title compound as a yellow oil (0.3g, 27.45%); [APCI MS] m/z 319 (MH^+).

Intermediate 26 : 2-[2-(4-trifluoromethoxyphenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



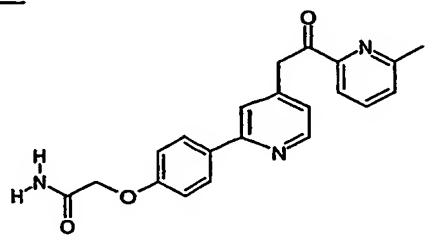
A mixture of intermediate 19 (2g, 7 mmol) and 4-trifluoromethoxyphenylboronic acid (1.55g, 7.7mmol) were reacted as described for intermediate 20 to afford the title compound as a yellow powder (1.6g, 62.58%); m.p. 76-78°C.

Intermediate 27 : 2-[2-(4-(2-(pyrolidin-1-yl)ethoxy)phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



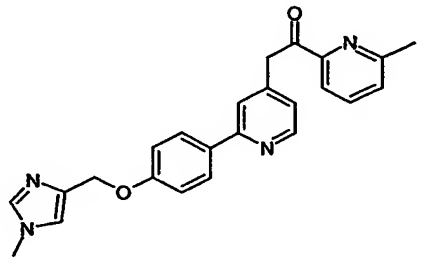
A mixture of intermediate 19 (1g, 3.4 mmol) and intermediate 8 (1.2g, 3.8mmol) were reacted as described for intermediate 20 to afford the title compound as a yellow oil (0.3g, 21.8%); [APCI MS] m/z 402 (MH^+).

Intermediate 28 : 2-[2-(4-(aminocarbonylmethyloxy)phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



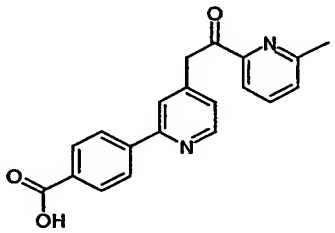
A mixture of intermediate 19 (2g, 6.9 mmol) and intermediate 9 (2.1g, 7.6 mmol) were reacted as described for intermediate 20 to afford the title compound as a brown powder (1.2g, 48.37%); m.p. 144-146°C.

Intermediate 29 : 2-[2-(4-(1-methyl-imidazol-4-yl)-phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



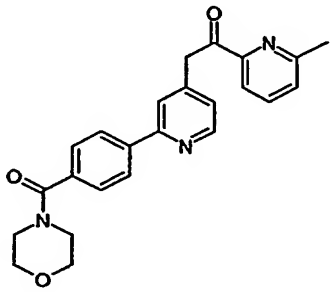
A mixture of intermediate 19 (0.357g, 1.22 mmol) and intermediate 10 (0.5g, 1.59 mmol) were reacted as described for intermediate 20 to afford the title compound as a yellow oil (0.15g, 30%); [APCI MS] m/z 399 (MH^+).

Intermediate 30: 2-[2-(4-(carboxy)-phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



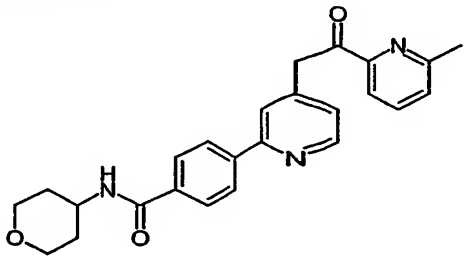
To a solution of intermediate 23 (1.2g, 3.47mmol) in MeOH (100ml) was added sodium hydroxide (solution 1N, 5ml, 5.2mmol) and the mixture was heated under reflux for 48 hours. After cooling, a solution of 1N HCl (5 ml) was added and the precipitate was filtered and dried. The titled compound was obtained as an orange solid (0.8g, 69.5%); [APCI MS] m/z 333 (MH^+).

Intermediate 31 : 2-[2-(4-((morpholin-4-yl)carbonyl)-phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



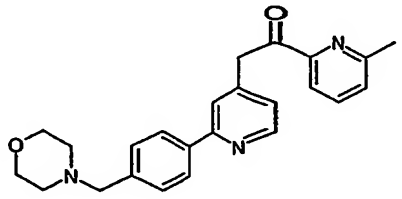
To a solution of intermediate 30 (0.8g, 2.41 mmol) in CH_2Cl_2 (50ml) were added morpholine (0.32ml, 3.61mmol), HOBT (0.49g, 3.61 mmol), EDCI (0.63g, 3.61 mmol), triethylamine (0.84ml, 6 mmol) and the mixture was stirred at room temperature for 24 hours and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH (90:10). The title compound was obtained as an orange oil (0.8g, 85.35%); [APCI MS] m/z 390 (MH^+).

Intermediate 32 : 2-{2-[4-((tetrahydropyran-4-yl)-aminocarbonyl)-phenyl]pyridin-4-yl}-1-(6-methylpyridin-2-yl)-ethanone



Intermediate 30 (1g, 3mmol) and 4-amino-tetrahydropyran (340mg, 3.3mmol) were reacted as described for intermediate 31 to afford, after chromatography on silicagel (CH_2Cl_2/MeOH, 90:10), the title compound as a yellow oil (0.3g, 24%); ^1H NMR (300MHz, $CDCl_3$, ppm) δ : 8.58 (d, 1H), 7.98 (m, 2H), 7.8 (m, 3H), 7.66 (m, 2H), 7.29 (m, 1H), 7.19 (m, 1H), 6.01 (m, 1H), 4.57 (s, 2H), 4.15 (m, 1H), 3.93 (m, 2H), 3.48 (m, 2H), 2.6 (s, 3H), 1.95 (m, 2H), 1.55 (m, 2H).

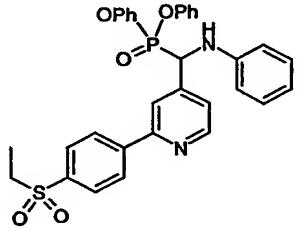
Intermediate 33: 2-[2-(4-((morpholin-4-yl)methyl)-phenyl)-pyridin-4-yl]-1-(6-methylpyridin-2-yl)-ethanone



To a solution of intermediate 24 (1g, 3.2mmol) in CH_2Cl_2 (100ml) were added morpholine (0.36g, 4.1mmol) and sodium triacetoxyborohydride (0.88g, 4.1mmol) and the mixture was stirred at room temperature for 3 hours and then poured into a saturated solution of $NaHCO_3$. After extraction with CH_2Cl_2, the organic phase was

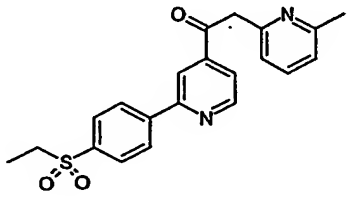
dried over Na_2SO_4, and concentrated under reduced pressure. The titled compound was obtained as a yellow oil (1.1g, 89.82%); [APCI MS] m/z 388 (MH^+).

Intermediate 34 : [(2-(4-ethanesulfonylphenyl)-pyridin-4-yl)-(phenylamino)-methyl]-phosphonic acid diphenylester



To a solution of 2-chloro-pyridine-4-carboxaldehyde (1g, 7.06mmol) in DME (50ml) was added 4-(ethanesulfonyl)-phenyl boronic acid (1.97g, 9.18 mmol), tetrakis(triphenylphosphine)palladium(0) (0.816g, 0.7mmol), Na_2CO_3 (solution 2M, 7ml) and the mixture was heated under reflux overnight and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4, and concentrated under reduced pressure.The residue was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH (99/1) to afford 2-(4-ethanesulfonylphenyl)-pyridine-4-carboxaldehyde as a yellow oil (1.94g, 98%). To a solution of 2-(4-ethanesulfonylphenyl)-pyridine-4-carboxaldehyde (1.94g, 7.06 mmol) in iPrOH were added aniline (0.772ml, 8.47 mmol) and diphenylphosphite (1.91ml, 9.9 mmol) and the mixture was stirred at room temperature for 18 hours and then concentrated under reduced pressure. The residue was treated with water and extracted with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and concentrated. After chromatography on silicagel (CH_2Cl_2), the title compound was obtained as a yellow oil (1.45g, 35.13%); [APCI MS] m/z 585 (MH^+).

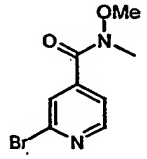
Intermediate 35: 1-[2-(4-ethanesulfonylphenyl)-pyridin-4-yl]-2-[6-methyl-pyridin-2-yl]-ethanone



To a solution of intermediate 34 (1.45g, 2.48 mmol) in THF/iPrOH were added 6-methyl-pyridine-2-carboxaldehyde (0.251g, 2.07 mmol) and cesium carbonate (1.35g, 4.14 mmol) and the mixture was stirred at room temperature for 18 hours and

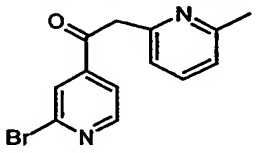
then neutralised with a solution of sodium bicarbonate. After concentration under reduced pressure, the residue was treated with water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. After chromatography on silica gel (CH_2Cl_2/MeOH, 99:1), the title compound was obtained as a yellow oil (0.321g, 34.02%); [APCI MS] m/z 381 (MH^+).

Intermediate 36: 2-bromo-N-methoxy-N-methyl-4-pyridinecarboxamide



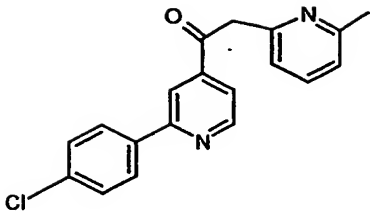
To a suspension of 2-bromo-4-pyridinecarboxylic acid (23.5g, 116mmol) in CH_2Cl_2 (600mL) were added under nitrogen HOBT (17.3g, 128mmol), EDCI (24.5g, 128mmol), triethylamine (46.85g, 464mmol) and N,O-dimethylhydroxylamine hydrochloride (17.02g, 175mmol). The reaction mixture was stirred at room temperature for 3h and then partitioned between water and CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford the title compound as a white solid (17g, 59.64 %); [APCI MS] m/z 246 (MH+).

Intermediate 37: 1-[2-bromo-pyridin-4-yl]-2-[6-methyl-pyridin-2-yl]-ethanone



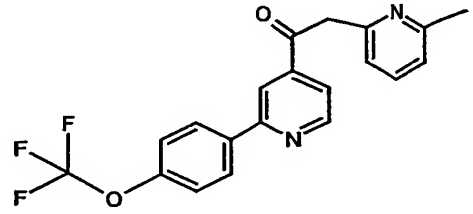
2,6-Lutidine (4.28g; 40mmol) was dissolved in dry THF (100mL) under nitrogen and the solution was cooled to -30°C. 2.5M n-Butyllithium in hexanes (16mL; 40mmol) was added at -30°C, then the mixture was stirred 1.5h at ambient temperature before being cooled to -30 to -40°C. A solution of intermediate 36 (4.9g; 20mmol) in dry THF (20mL) was added at -40°C and the reaction stirred for 2h. Saturated aqueous ammonium chloride was added and the mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure . The residue was purified by chromatography on silica gel (CH_2Cl_2/ MeOH , 99 /1) to give the title compound (3.42g; 58%) as a yellow solid; m.p. 126°C; [APCI MS] m/z 292 (MH^+).

Intermediate 38: 2-(6-methylpyridin-2-yl)-1- [2-(4-chlorophenyl)-pyridin-4-yl]-ethanone



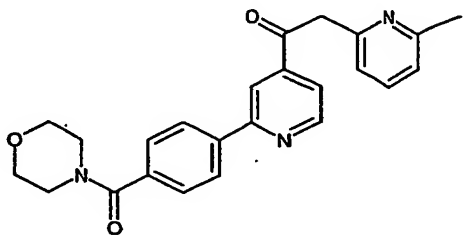
To a solution of intermediate 37 (0.582g, 2mmol) in a mixture DME (30ml) / water (15ml) were added 4-chloro-phenyl boronic acid (0.405g, 2.6mmol), tetrakis(triphenylphosphine) palladium(0) (0.06g, mmol) and sodium carbonate solution (2M, 4ml). The reaction mixture was heated for 30min and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to afford the title compound as a solid (0.415g, 64.44%); m.p. 94°C; [APCI MS] m/z 323 (MH^+).

Intermediate 39: 2-(6-methylpyridin-2-yl)-1- [2-(4-trifluoromethoxyphenyl)-pyridin-4-yl]-ethanone



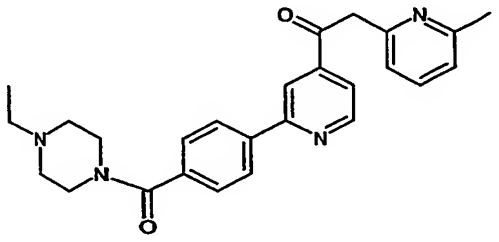
Intermediate 37 (0.582g, 2 mmol) and 4-trifluoromethoxy-phenyl boronic acid (0.533g, 2.6 mmol) were reacted as was described for intermediate 38 to give the title compound as a solid (0.72g, 96.77%); m.p. 60°C; [APCI MS] m/z 373 (MH^+).

Intermediate 40: 2-(6-methylpyridin-2-yl)-1- [2-(4-((morpholin-4-yl)carbonyl)phenyl)-pyridin-4-yl]-ethanone



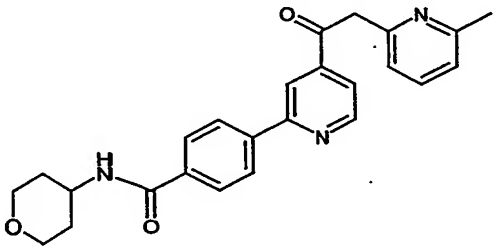
Intermediate 37 (1g, 3.43 mmol) and intermediate 12 (1.2g, 3.78 mmol) , were reacted as was described for intermediate 38 to give the title compound as a yellow solid (1.25g, 90.71%); m.p. 106°C; [APCI MS] m/z 402 (MH^+).

Intermediate 41: 2-(6-methylpyridin-2-yl)-1- [2-(4-((1-ethyl-piperazin-4-yl)carbonyl)phenyl)-pyridin-4-yl]-ethanone



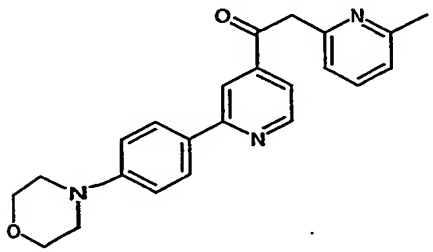
Intermediate 37 (1g, 3.43 mmol) and intermediate 14 (1.28g, 3.78 mmol) were reacted as was described for intermediate 38 to give the title compound as a yellow solid (0.95g, 64.59%); m.p. 90°C; [MS APCI] m/z 429 (MH^+).

Intermediate 42: 2-(6-methylpyridin-2-yl)-1- [2-(4-((tetrahydropyran-4-yl)-aminocarbonyl)phenyl)-pyridin-4-yl]-ethanone



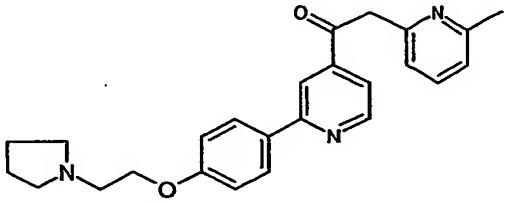
Intermediate 37 (1g, 3.43 mmol) and intermediate 13 (1.25g, 3.78 mmol) were reacted as was described for intermediate 38 to give the title compound as a yellow solid (1.4g, 98.17%); m.p. 210°C; [APCI MS] m/z 416 (MH^+).

Intermediate 43: 2-(6-methylpyridin-2-yl)-1- [2-(4-(morpholin-4-yl)phenyl)-pyridin-4-yl]-ethanone



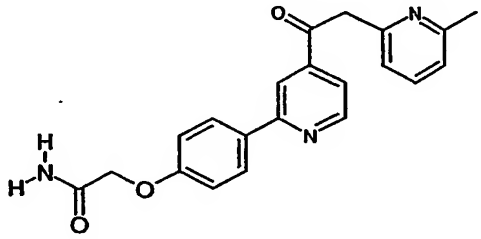
Intermediate 37 (1g, 3.43 mmol) and intermediate 7 were reacted as was described for intermediate 38 to give the title compound as a yellow solid (1.2g, 84%); m.p. 114°C; [APCI MS] m/z 374 (MH^+).

Intermediate 44: 2-(6-methylpyridin-2-yl)-1- [2-(4-(2-(pyrolidin-1-yl)-ethoxy)-phenyl)-pyridin-4-yl]-ethanone



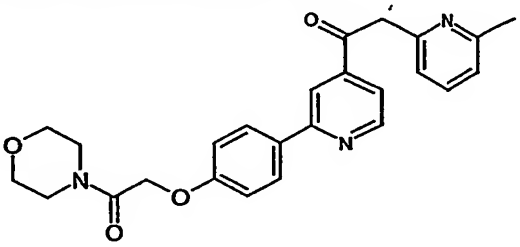
Intermediate 37 (1g, 3.43 mmol) and intermediate 8 (1.2g, 3.78 mmol) were reacted as was described for intermediate 38 to give, after chromatography on silica gel (CH_2Cl_2/MeOH, 90:10), the title compound as a yellow oil (0.8g, 58%); [APCI MS] m/z 402 (MH^+).

Intermediate 45: 2-(6-methylpyridin-2-yl)-1- [2-(4-(aminocarbonylmethyloxy)-phenyl)-pyridin-4-yl]-ethanone



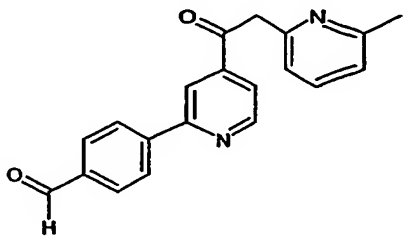
Intermediate 37 (1g , 3.43 mmol) and intermediate 9 (0.93g, 4.12 mmol) were reacted as was described for intermediate 38 to give the title compound as a yellow solid (1.2g, 96%); m.p. 168°C; [APCI MS] m/z 362 (MH^+).

Intermediate 46 : 2-(6-methylpyridin-2-yl)-1- [2-(4-((morpholin-4-yl)-carbonylmethyloxy)-phenyl)-pyridin-4-yl]-ethanone



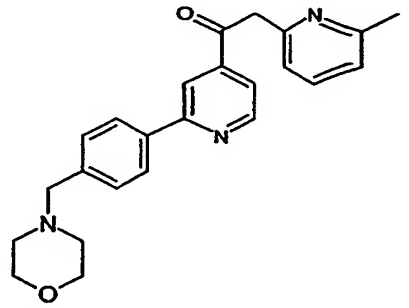
Intermediate 37 (1g, 3.43 mmol) and intermediate 11 (1.45g, 4.12 mmol) were reacted as was described for intermediate 38 to give, after chromatography on silica gel (CH_2Cl_2/MeOH, 98:2), the title compound as a yellow gum (1g, 67.52%); [APCI MS] m/z 432 (MH^+).

Intermediate 47: 2-(6-methylpyridin-2-yl)-1- [2-(4-formylphenyl)-pyridin-4-yl]-ethanone



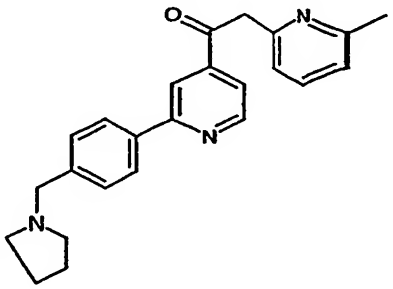
Intermediate 37 (2g, 7 mmol) and 4-formylphenylboronic acid (1.34g, 9 mmol) were reacted as was described for intermediate 38 to give the title compound as a yellow solid (2.1g, 96.69%); m.p. 118°C; [APCI MS] m/z 317 (MH^+).

Intermediate 48: 2-(6-methylpyridin-2-yl)-1- [2-(4-((morpholin-4-yl)methyl)-phenyl)-pyridin-4-yl]-ethanone



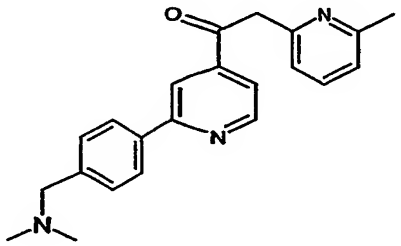
To a solution of intermediate 47 (0.984g, 3 mmol) in 1,2-dichloroethane (40 ml) were added morpholine (0.34g, 3.9 mmol), sodium triacetoxyborohydride (0.826g, 3.9 mmol) and acetic acid (0.216g, 3.6 mmol) and the mixture was stirred at room temperature for 3 hours and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The title compound was obtained as an oil (1.1g, 91%); [APCI MS] m/z 388 (MH^+).

Intermediate 49: 2-(6-methylpyridin-2-yl)-1- [2-(4-((pyrolidin-1-yl)methyl)-phenyl)-pyridin-4-yl]-ethanone



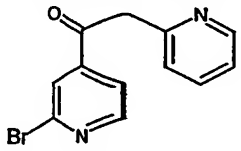
Intermediate 47 (0.7g, 2.2 mmol) and pyrolidine (0.203g, 2.8 mmol) were reacted as described for intermediate 48, to afford after chromatography on silica gel (CH_2Cl_2/MeOH, 90:10), the title compound as a yellow gum (0.5g, 60.84%); [APCI MS] m/z 372 (MH^+).

Intermediate 50: 2-(6-methylpyridin-2-yl)-1- [2-(4-((dimethylamino)methyl)-phenyl)-pyridin-4-yl]-ethanone



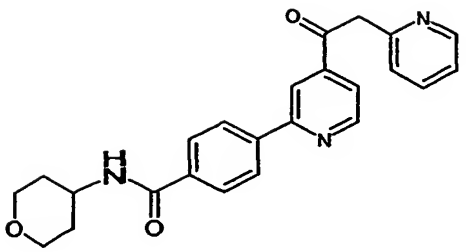
Intermediate 47 (0.7g, 2.2 mmol) and dimethylamine (solution 2M in THF, 1.4ml, 2.86 mmol) were reacted as described for intermediate 48, to afford after chromatography on silica gel (CH_2Cl_2/MeOH, 9/1), the title compound as a yellow gum (0.4g, 52.34%); [APCI MS] m/z 346 (MH^+).

Intermediate 51: 1-[2-bromo-pyridin-4-yl]-2-[pyridin-2-yl]-ethanone



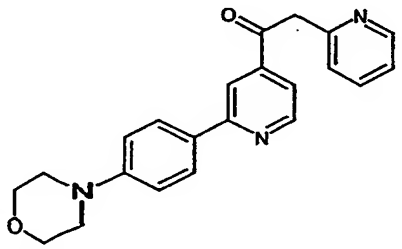
To a solution of 6-methylpyridine (2.79g; 30 mmol) in dry THF (20ml) under nitrogen cooled at -80°C, was added dropwise NaHMDS (solution 1M/THF, 36 ml, 36 mmol). and the mixture was stirred for 1hour at -80°C. A solution of intermediate 36 (7.35g; 30 mmol) in dry THF (10mL) was added dropwise and the mixture was then stirred at room temperature overnight and then concentrated under reduced pressure. The residue was treated with hexane and the resulting precipitate was filtered. The solid was then diluted with saturated ammonium chloride solution and the aqueous phase extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. After chromatography on silica gel (CH_2Cl_2/MeOH, 98:2), the title compound was obtained as a yellow solid (4.1g, 49.34%); m.p. 96°C.

Intermediate 52: 2-(pyridin-2-yl)-1- [2-(4-((tetrahydropyran-4-yl)aminocarbonyl)-phenyl)-pyridin-4-yl]-ethanone



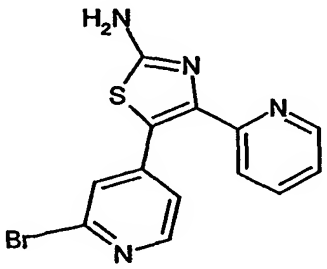
Intermediate 51 (0.95g, 3.43 mmol) and intermediate 13 (1.25g, 3.78 mmol) were reacted as described for intermediate 38 to afford, after chromatography on silica gel (CH_2Cl_2/MeOH, 97:3), the title compound as a yellow solid (0.8g, 58.17%); [APCI MS] m/z 402 (MH^+).

Intermediate 53: 2-(pyridin-2-yl)-1- [2-(4-(morpholin-4-yl)-phenyl)-pyridin-4-yl]-ethanone



Intermediate 51 (0.95g, 3.43 mmol) and intermediate 7 (1.11g, 3.78 mmol) were reacted as described for intermediate 38 to afford , after chromatography on silica gel (CH_2Cl_2/MeOH, 96:4), the title compound as a yellow solid (0.6g, 48.73%); [APCI MS] m/z 360 (MH^+).

Intermediate 54: Solid supported 5-(2-bromo-4-pyridinyl)-4-(2-pyridinyl)-1,3-thiazol-2-amine



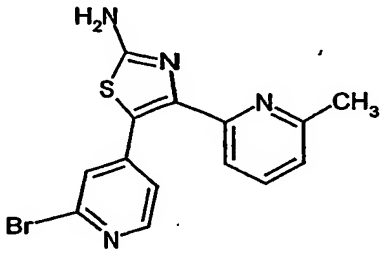
Step 1: Rink Argopore resin (12g, 0.58 mmol/g substitution) was placed into a peptide vessel and washed with CH_2Cl_2 (3x100mL). The resin was then treated for 10min with a solution of piperidine 20% in DMF (3x40mL). After washing with DMF

(3x100mL) and CH_2Cl_2 (3x100mL), the resin was treated with a solution of Fmoc-NCS (0.2M) in CH_2Cl_2 (170mL) under argon at room temperature for 1h. The resin was washed with DMF (3x100mL), EtOH (3x100mL) and CH_2Cl_2 (3x100mL) and subsequently stirred for 10min with a solution of piperidine 20% in DMF (3x40mL) to give after washing with DMF (3x100mL) and CH_2Cl_2 (3x100mL) the resin bound thiourea.

Step 2: To a solution of intermediate 18 (8.5g, 29mmol) in dioxane (145mL) was added under argon polymer-supported pyridinium perbromide (1.8mmol/g, 16g). The suspension was shaken under argon at room temperature overnight. The resin was removed by filtration and washed with dioxane (25mL) to give 2-bromo-2-(2-bromo-4-pyridinyl)-1-(2-pyridinyl)ethanone which was used in solution in dioxane without purification in the next step.

Step 3: The product from step 1 was stirred with 2-bromo-2-(2-bromo-4-pyridinyl)-1-(2-pyridinyl)ethanone (0.18M) in dioxane (175mL) for 4h at room temperature under argon. The resin was washed with dioxane (3x100mL). A second exposure with 2-bromo-2-(2-bromo-4-pyridinyl)-1-(2-pyridinyl)ethanone (0.18M in dioxane, 175mL) was performed. The resin was washed with DMF (3x100mL), EtOH (3x100mL), CH_2Cl_2 (3x100mL) and dried under a stream of nitrogen overnight. 2 mg of the obtained resin were cleaved with a solution of TFA 20% in CH_2Cl_2 to give the title compound which was characterised by LC-MS (purity>96%); [APCI MS] m/z 333, 335, 336 (MH+).

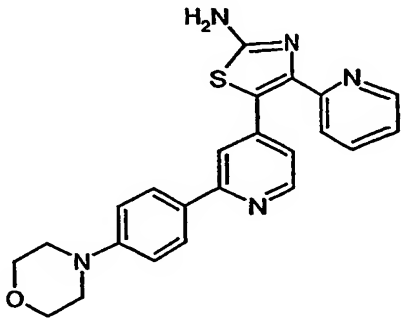
Intermediate 55: Solid supported 5-(2-bromo-4-pyridinyl)-4-(6-methyl-2-pyridinyl)-1,3-thiazol-2-amine



Intermediate 55 was prepared in analogous fashion to intermediate 54 starting from intermediate 19. After step 3, 2 mg of the obtained resin were cleaved with a solution of TFA 20% in CH_2Cl_2 to give the title compound which was characterised by LC-MS (purity>96%); [APCI MS] m/z 347/ 349/ 350 (MH+).

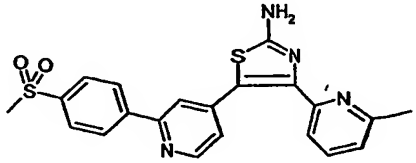
Examples

Example 1: 5-{2-[4-(morpholin-4-yl)phenyl]pyridin-4-yl}-4-(pyridin-2-yl)-1,3-thiazol-2-amine



To a solution of Intermediate 17 (0.4 g, 1.11 mmol) in CH_2Cl_2 (20 ml) was added polymer-supported pyridinium perbromide (Fluka, 0.62g, 1eq, 1.11 mmol) and the suspension shaken for 50 min. The resin was removed by filtration, with the filtrate being added directly to thiourea (0.25 g, 3 eq, 3.33 mmol) and the resin washed several times with ethanol. The filtrate was heated at reflux overnight, allowed to cool at room temperature and concentrated. The residue was basified with aqueous NaOH, extracted into CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. After chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 then 90:10) and crystallisation from ethyl acetate, the title compound was obtained as cream crystals (108 mg, 23.35%); m.p. 246°C; [APCI MS] m/z 416 MH^+.

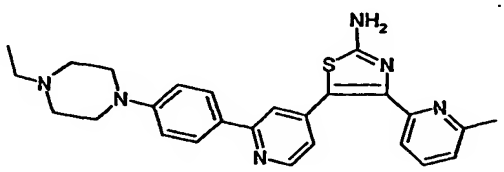
Example 2: 5-{2-[4-(methanesulfonyl)phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



To a solution of Intermediate 20 (1.1 g, 3 mmol) in CH_2Cl_2 (100 ml) was added polymer-supported pyridinium perbromide (3g) and the suspension was shaken for 3 hours. The resin was removed by filtration, with the filtrate being added directly to thiourea (0.3 g, 3.9 mmol) and the resin washed many times with ethanol. The filtrate was heated under reflux for 4 hours, allowed to cool and concentrated. The residue was basified with aqueous NaOH, extracted into CH_2Cl_2 and this phase washed with water. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. After chromatography on silica gel (CH_2Cl_2/MeOH, 90:10) and trituration with pentane, the title compound was obtained as a solid (0.9g, 71%); m.p. 236-

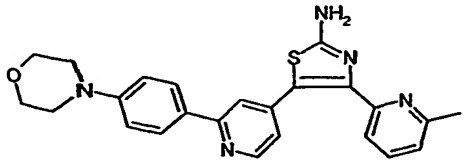
238°C; TOF MS ES$^+$ exact mass calculated for $C_{21}H_{18}N_4O_2S_2$: calculated 423.0949 (MH^+). Found 423.0945(MH^+).

Example 3: 5-{2-[4-(4-ethylpiperazin-1-yl)phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



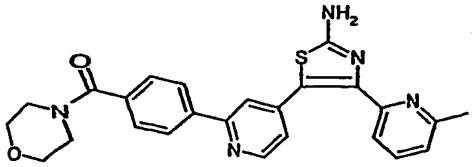
Intermediate 21 (0.5g, 1.3mmol) was reacted as described for example 1, to afford after crystallisation from EtOH the title compound as crystals (0.16g, 27.1%); m.p. 230-232°C; TOF MS ES$^+$ exact mass calculated for $C_{26}H_{28}N_6S$: calculated 457.2174 (MH^+). Found 457.2213 (MH^+).

Example 4: 5-{2-[4-(morpholin-4-yl)phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



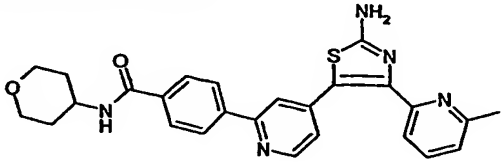
Intermediate 22 (1.2g, 3.2mmol) was reacted as described for example 1, to afford after crystallisation from MeOH the title compound as cream crystals (400mg, 28.98%); m.p. 250-252°C; TOF MS ES$^+$ exact mass calculated for $C_{24}H_{23}N_5OS$ calculated 430.1701 (MH^+). Found 430.1698 (MH^+).

Example 5 : 5-{2-[4-((morpholin-4-yl)carbonyl)phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



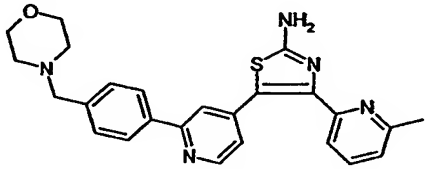
Intermediate 31(0.8g, 2mmol) was reacted as described for example 1 to afford, after crystallisation from acetonitrile the titled compound as cream crystals (300mg, 32%); m.p. 158-160°C; [LC Tof] $C_{25}H_{23}N_5O_2S_1$ (MH^+) calculated 458.1651 (MH^+) found 458.1602; -4.9ppm.

Example 6: 5-{2-[4-((tetrahydropyran-4-yl)-aminocarbonyl)-phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



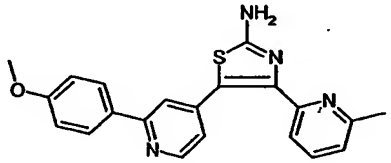
Intermediate 32 (0.3g, 0.72mmol) was reacted as described for example 1 to afford after trituration with pentane, the title compound as cream crystals (0.14g, 41.12%); m.p. 230-232°C; [APCI MS] m/z 472 (MH^+).

Example 7: 5-{2-[4-((morpholin-4-yl)methyl)phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



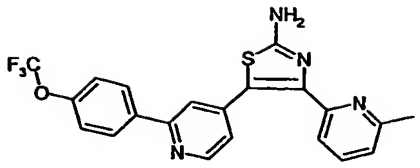
Intermediate 33 (1.1g, 2.54mmol) was reacted as described for example 1, to afford after crystallisation from EtOH the title compound as cream crystals (0.2g, 15.9%); m.p. 190-192°C; TOF MS ES^+ exact mass calculated for $C_{25}H_{25}N_5OS$: 443.1860 (MH^+).Found 443.1800 (MH^+).

Example 8 : 5-{2-[4-methoxyphenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



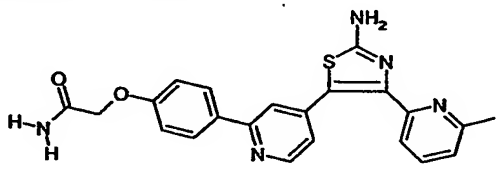
Intermediate 25 (0.3g, 0.94mmol) was reacted as described for example 1, to afford after crystallisation from acetonitrile the title compound as cream crystals (0.11g, 31.18%); m.p. 188-190°C; [APCI MS] m/z 375 (MH^+).

Example 9: 5-{2-[4-trifluoromethoxyphenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



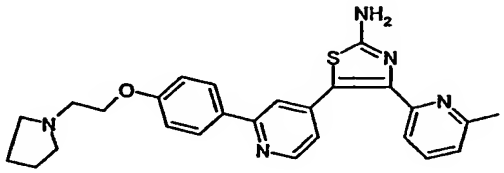
Intermediate 26 (1.6g, 4.3mmol) was reacted as described for example 1 to afford, after trituration with diisopropyl oxide, the title compound as a white solid (1.2g, 65.19%); m.p. 222-224°C; [APCI MS] m/z 429 (MH^+).

Example 10: 5-{2-[4-(aminocarbonylmethyloxy)-phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



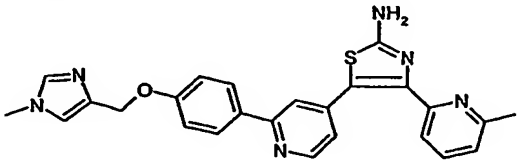
Intermediate 28 (1.2g, 3.3mmol) was reacted as described for example 1 to afford, after crystallisation from acetonitrile, the title compound as yellow crystals (0.2g, 14.43%); m.p. 52-154°C; [APCI MS] m/z 418 (MH^+).

Example 11: 5-{2-[4-(2-(pyrrolidin-1-yl)-ethoxy)-phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



Intermediate 27 (0.3g, 0.75mmol) was reacted as described for example 1 to afford, after trituration with pentane, the title compound as cream crystals (0.11g, 32.17%); m.p. 176-178°C; [APCI MS] m/z 458 (MH^+).

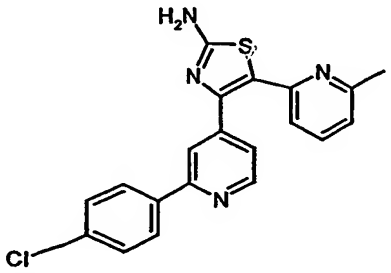
Example 12: 5-{2-[4-((1-methyl-imidazol-4-yl)methyloxy)-phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine



Intermediate 29 (0.15g, 0.37mmol) was reacted as described for example 1 to afford, after trituration with diisopropyl oxide, the title compound as a yellow solid (0.03mg,

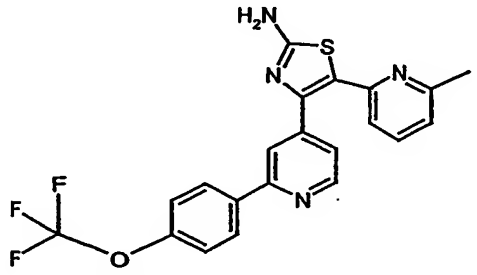
17.5%); m.p. 226-228°C; TOF MS ES$^+$ exact mass calculated for $C_{25}H_{22}N_6OS$: 455.1654 (MH^+). Found 454.1600(MH^+).

Example 13: 4-[2-(4-chlorophenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



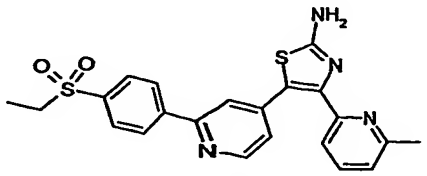
To a solution of Intermediate 38 (0.322 g, 1 mmol) in THF (10 ml) was added polymer-supported pyridinium perbromide (0.66g, 1 mmol) and the suspension was shaken for 3 hours at room temperature. The resin was removed by filtration, with the filtrate being added directly to thiourea (0.152 g, 2 mmol) and the resin washed many times with ethanol. The filtrate was heated under reflux for 3 hours, allowed to cool and concentrated. Water was added to the residue and the resulting precipitate was filtered and dried. After crystallisation from EtOH, the title compound was obtained as white crystals (0.154g, 40.74%); m.p. 222°C; TOF MS ES$^+$ exact mass calculated for $C_{20}H_{15}ClN_4S$: 379.0784 (MH+). Found 379.0772 (MH^+).

Example 14: 4-[2-(4-trifluoromethoxyphenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



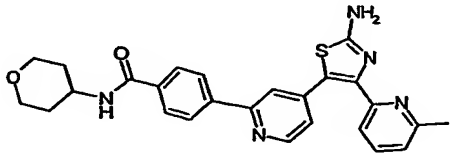
Intermediate 39 (0.372g, 1 mmol) was reacted as described for example 13 to afford, after crystallisation from EtOH, the title compound as white crystals (0.17g, 39.72%); m.p. 232°C; TOF MS ES$^+$ exact mass calculated for $C_{21}H_{15}F_3N_4OS$: 429.0997 (MH+) . Found 429.0958 (MH+).

Example 15: 4-[2-(4-(ethanesulfonyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



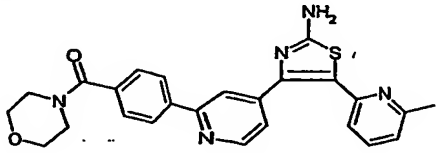
Intermediate 35 (0.321g, 0.84 mmol) was reacted as described for example 13 to afford, after trituration with CH_2Cl_2, the title compound as a white solid (0.015g, 4.1%); m.p. 219°C; TOF MS ES$^+$ exact mass calculated for $C_{22}H_{20}N_4O_2S_2$: 437.1106 (MH+). Found 437.1096 (MH+).

Example 16: 4-[2-(4-((tetrahydropyran-4-yl)-aminocarbonyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



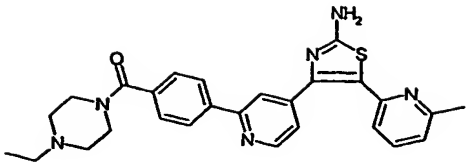
Intermediate 42 (0.8g, 2 mmol) was reacted as described for example 13 to afford, after crystallisation from EtOH, the title compound as crystals (0.202g, 22.25%); m.p. 283°C; TOF MS ES$^+$ exact mass calculated for $C_{26}H_{25}N_5O_2S$: 472.1807 (MH+). Found 472.1815 (MH+).

Example 17: 4-[2-(4-((morpholin-4-yl)carbonyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



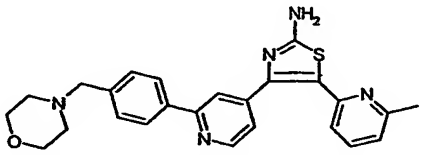
Intermediate 40 (0.6g, 1.5 mmol) was reacted as described for example 13 to afford, after crystallisation EtOH, the title compound as yellow crystals (0.265g, 38.66%); m.p. 246°C; TOF MS ES$^+$ exact mass calculated for $C_{25}H_{23}N_5O_2S$: 458.1651 (MH+). Found 458.1610 (MH+).

Example 18: 4-[2-(4-(1-ethyl-piperazin-4-yl)carbonyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



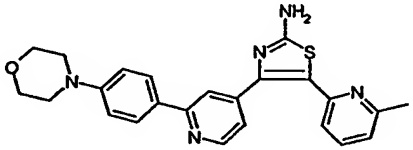
Intermediate 41(0.428g, 1 mmol) was reacted as described for example 13 to afford, after crystallisation from EtOH, the title compound as yellow crystals (0.2g, 41.32%); m.p. 224°C; TOF MS ES$^+$ exact mass calculated for $C_{27}H_{28}N_6OS$: 485.2123 (MH+). Found 485.2128 (MH+).

Example 19: 4-[2-(4-((morpholin-4-yl)methyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



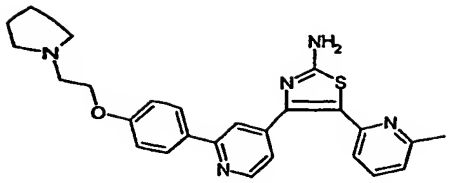
Intermediate 48 (0.58g, 1.5 mmol) was reacted as described for example 13 to afford, after crystallisation from EtOH, the title compound as yellow crystals (0.33g, 50%); m.p. 236°C; TOF MS ES$^+$ exact mass calculated for $C_{25}H_{25}N_5OS$: :444.1858 (MH+). Found 444.1862 (MH+).

Example 20: 4-[2-(4-(morpholin-4-yl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



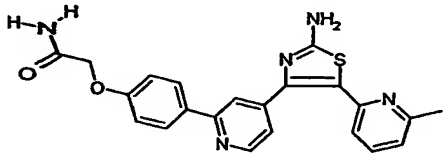
Intermediate 43 (0.379g, 1 mmol) was reacted as described for example 13 to afford, after crystallisation from acetonitrile, the title compound as yellow crystals (0.148g, 34%); m.p. 246°C; TOF MS ES$^+$ exact mass calculated for $C_{24}H_{23}N_5OS$: 430.1701 (MH+). Found 430.1648 (MH+).

Example 21: 4-[2-(4-(2-(pyrolidin-1-yl)-ethoxy)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



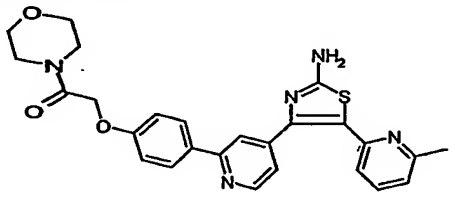
Intermediate 44 (0.4g, 1 mmol) was reacted as described for example 13 to afford, after crystallisation from ethyl acetate, the title compound as white crystals (0.225g, 49.36%); m.p. 150°C; TOF MS ES$^+$ exact mass calculated for $C_{26}H_{27}N_5OS$: 458.2014 (MH+). Found 458.1963 (MH+).

Example 22: 4-[2-(4-(aminocarbonylmethyloxy)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



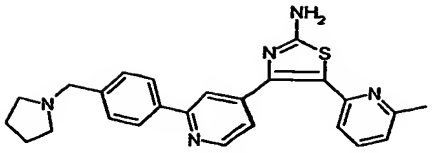
Intermediate 45 (0.542g, 1.5 mmol) was reacted as described for example 13 to afford, after crystallisation from EtOH, the title compound as yellow crystals (0.14g, 22.36%); m.p. 191°C; TOF MS ES$^+$ exact mass calculated for $C_{22}H_{19}N_5O_2S$: 418.1338 (MH+). Found 418.1289 (MH+).

Example 23: 4-[2-(4-((morpholin-4-yl)carbonylmethyloxy)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



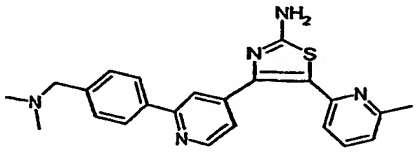
Intermediate 46 (0.431g, 1 mmol) was reacted as described for example 13 to afford, after crystallisation from toluene, the title compound as white crystals (0.26g, 53.39%); m.p. 172°C; TOF MS ES$^+$ exact mass calculated for $C_{26}H_{25}N_5O_3S$ (MH+) calculated 488.1756 (MH+). Found 488.1700 (MH+).

Example 24: 4-[2-(4-((pyrrolidin-1-yl)methyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



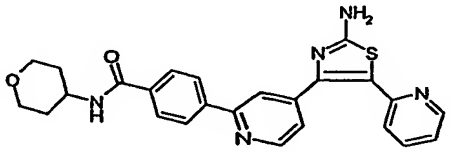
Intermediate 49 (0.5g, 1.35 mmol) was reacted as described for example 13 to afford, after crystallisation from EtOH, the title compound as crystals (0.194g, 33.71%); m.p. 200°C; TOF MS ES$^+$ exact mass calculated for $C_{25}H_{25}N_5S$ (MH+) calculated 428.1909 (MH+). Found 428.1861 (MH+).

Example 25: 4-[2-(4-((dimethylamino)methyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine



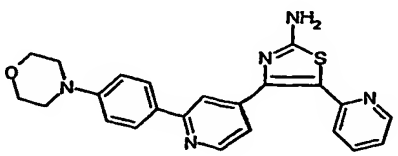
Intermediate 50 (0.4g, 1.16 mmol) was reacted as described for example 13 to afford, after crystallisation from EtOH, the title compound as crystals (0.176g, 37.86%); m.p. 210°C; TOF MS ES$^+$ exact mass calculated for $C_{23}H_{23}N_5S$ (MH+) calculated 402.1752 (MH+). Found 402.1707 (MH+).

Example 26: 4-[2-(4-((tetrahydropyran-4-yl)aminocarbonyl)phenyl)pyridin-4-yl]-5-[pyridin-2-yl]-1,3-thiazol-2-amine



Intermediate 52 (0.4g, 1.16 mmol) was reacted as described for example 13 to afford, after crystallisation from EtOH, the title compound as yellow crystals (0.395g, 43.32%); m.p. 268°C; TOF MS ES$^+$ exact mass calculated for $C_{25}H_{23}N_5O_2S$ (MH+) calculated 458.1651 (MH+). Found 458.1637 (MH+).

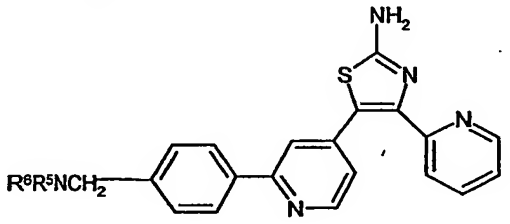
Example 27: 4-[2-(4-(morpholin-4-yl)phenyl)pyridin-4-yl]-5-[pyridin-2-yl]-1,3-thiazol-2-amine



Intermediate 53 (0.6g, 1.67 mmol) was reacted as described for example 13 to afford, after crystallisation from EtOH, the title compound as yellow crystals (0.179g, 25.81%); m.p. 276°C; TOF MS ES$^+$ exact mass calculated for $C_{23}H_{21}N_5OS$: calculated 416.1545 (MH+). Found 416.1504 (MH+).

Examples 28 to 30

Step 1: Intermediate 54 supported on resin (1g) was weighed out into a peptide vessel. Then 4-formylphenylboronic acid (870mg, 5.8mmol, 10eq), $Pd(PPh_3)_4$ (134 mg, 0.16mmol, 0.2eq), and sodium carbonate (615mg, 5.8mmol, 2M) were added and suspended in toluene/EtOH (8:2, 20mL). The reaction vessel was purged with argon for 5 min, and the mixture was stirred at 90°C for 16h. The resin was washed with DMF (3x10mL), water (3x10mL), EtOH (3x10mL) and CH_2Cl_2 (3x10mL).
Step 2: The product from step 1 was placed into a peptide vessel with a solution of NHR^5R^6 (5.8mmol, 10eq) in trimethylorthoformate (5.4mL). Then a solution of sodium cyanoborohydride (0.2M) in THF (5.4mL) with acetic acid (110µL) was added. The reaction vessel was purged with argon for 5 min and the mixture was stirred at 60°C for 16h. The resin was washed with DMF (3x10mL), EtOH (3x10mL) and CH_2Cl_2 (3x10mL). The resin was treated with a solution of 20% TFA in CH_2Cl_2 and the solvent was removed under reduced pressure. Purification of the residue by HPLC chromatography (water/ acetonitrile gradient) gave the products of formula (Id') shown in Table 1, i.e. compounds of general formula (I) where A is S, B is N, R^2 and R^3 are hydrogen and R^1 is $-CH_2NR^5R^6$.



(Id')

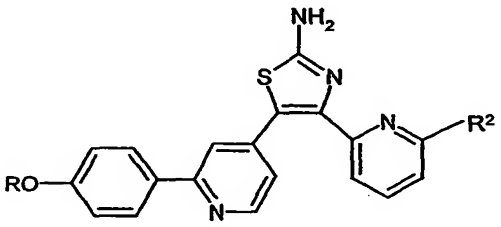
Table 1

Ex	R^5	R^6	Physical data
28	H	isopropyl	[APCI MS] m/z 402 MH+
29	$-(CH_2)_4-$		TOF MS ES$^+$ exact mass calculated for $C_{24}H_{23}N_5S$ (MH+): 414.1752. Found : 414.1766.
30	H	cyclobutyl	TOF MS ES$^+$ exact mass calculated for $C_{24}H_{23}N_5S$ (MH+): 414.1752. Found : 414.1749.

Examples 31 to 34

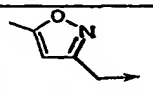
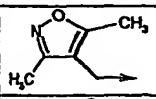
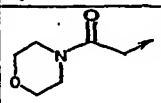
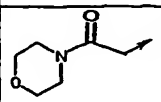
Step 1: Intermediate 54 or intermediate 55 supported on resin (1g) were weighed out into a peptide vessel. Then 4-hydroxyphenylboronic acid (800mg, 5.8mmol, 10eq), $Pd(PPh_3)_4$ (134 mg, 0.16mmol, 0.2eq), and sodium carbonate (615mg, 5.8mmol, 2M) were added and suspended in toluene/EtOH (8:2, 20mL).The reaction vessel was purged with argon for 5 min, and the mixture was stirred at 90°C for 16h. The resin was washed with DMF (3x10mL), water (3x10mL), EtOH (3x10mL) and CH_2Cl_2 (3x10mL).

Step 2: The product from step 1 was placed into a peptide vessel with a solution of R-Cl (5.8mmol, 10eq) in DMSO (10mL). Then a solution of potassium carbonate (802mg, 5.8mmol, 10eq) in DMSO (5mL) was added. The reaction vessel was purged with argon for 5 min and the mixture was stirred at 90°C for 16h. The resin was washed with DMF (3x10mL), EtOH (3x10mL) and CH_2Cl_2 (3x10mL). The resin was treated with a solution of 20% TFA in CH_2Cl_2 and the solvent was removed under reduced pressure. Purification of the residue by HPLC chromatography (water/ acetonitrile gradient) gave the products of formula (Ic') shown in Table 2, i.e. compounds of general formula (I) where A is S, B is N, R^3 is hydrogen, R^4 is NH_2 and R^1 is OR.



(Ic')

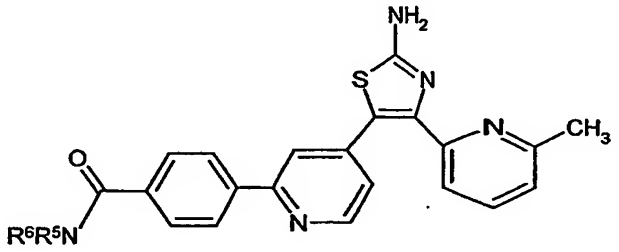
Table 2

Ex	R	R^2	From intermediate supported on resin	Physical data
31		methyl	55	TOF MS ES^+ exact mass calculated for $C_{25}H_{21}N_5O_2S$ (MH+): 456.1494. Found: 456.1457.
32		H	54	TOF MS ES^+ exact mass calculated for $C_{25}H_{21}N_5O_2S$ (MH+): 456.1494. Found: 456.1545.
33		methyl	55	TOF MS ES^+ exact mass calculated for $C_{26}H_{25}N_5O_3S$ (MH+): 488.1756. Found : 488.1792.
34		H	54	TOF MS ES^+ exact mass calculated for $C_{25}H_{23}N_5O_3S$ (MH+): 474.1600. Found : 474.1552.

Examples 35 to 46

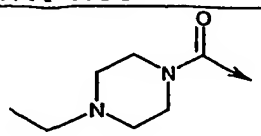
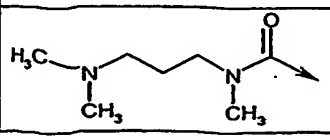
Step 1: Intermediate 55 supported on resin (1g) was weighed out into a peptide vessel. Then 4-methoxycarbonylphenylboronic acid (1.05g, 5.8mmol, 10eq), $Pd(PPh_3)_4$ (0.134 g, 0.16mmol, 0.2eq), and a aqueous solution of sodium carbonate (0.615g, 5.8mmol, 2M) were added and suspended in toluene/EtOH (8:2, 20mL). The reaction vessel was purged with argon for 5 min, and the mixture was stirred at 90°C for 16h. The resin was washed with DMF (3x10mL), water (3x10mL), EtOH (3x10mL) and CH_2Cl_2 (3x10mL). Then resin was added to a sodium hydroxide solution (2M) in dioxane (10mL). The reaction mixture was stirred at 50°C for 16h. The resin was washed with DMF (3x10mL), EtOH (3x10mL) and CH_2Cl_2 (3x10mL).

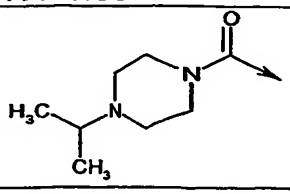
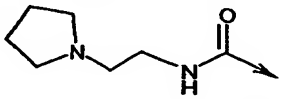
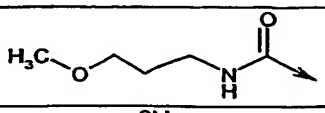
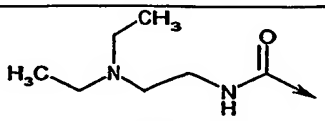
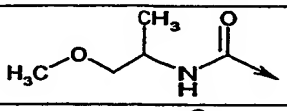
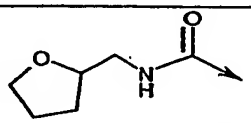
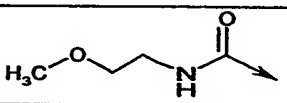
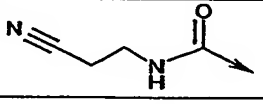
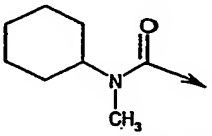
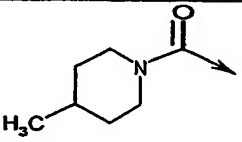
Step 2: The product from step 1 was placed into a peptide vessel with a solution of NHR^5R^6 (5.8mmol, 10eq) in DMF (5mL). Then a solution of HOBT (1.18g, 8.7mmol, 15eq) and EDCI (1.36mL, 8.7mmol, 15eq) in DMF (5mL) was added. The reaction vessel was purged with argon for 5 min and the mixture was stirred at 70°C for 16h. The resin was washed with DMF (3x10mL), EtOH (3x10mL), CH_2Cl_2 (3x10mL). The resin was treated with a solution of 20% TFA in CH_2Cl_2 and the solvent was removed under reduced pressure. Purification of the residue by HPLC chromatography (water/ acetonitrile gradient) gave the products of formula (Ie') shown in Table 3, i.e. compounds of general formula (I) where A is S, B is N, R^2 is methyl, R^3 is hydrogen, and R^1 is $-CONR^5R^6$.



(Ie')

Table 3

Ex	R^6R^5NCO-	Physical data
35		TOF MS ES^+ exact mass calculated for $C_{27}H_{28}N_6OS$ (MH+): 485.2123. Found :485.2123.
36		TOF MS ES^+ exact mass calculated for $C_{27}H_{30}N_6OS$ (MH+): 487.2280. Found :487.2267.

Ex	R^6R^5NCO-	Physical data
37		TOF MS ES^+ exact mass calculated for $C_{28}H_{30}N_6OS$ (MH+): 499.2280. Found :499.2277.
38		TOF MS ES^+ exact mass calculated for $C_{27}H_{28}N_6OS$ (MH+): 485.2123. Found :485.2094.
39		TOF MS ES^+ exact mass calculated for $C_{25}H_{25}N_5O_2S$ (MH+): 460.1807. Found :460.1810.
40		TOF MS ES^+ exact mass calculated for $C_{27}H_{30}N_6OS$ (MH+): 487.2280. Found :487.2260.
41		TOF MS ES^+ exact mass calculated for $C_{25}H_{25}N_5O_2S$ (MH+): 460.1807. Found :460.1799.
42		TOF MS ES^+ exact mass calculated for $C_{26}H_{25}N_5O_2S$ (MH+): 472.1807. Found :472.1798.
43		TOF MS ES^+ exact mass calculated for $C_{24}H_{23}N_5O_2S$ (MH+): 466.1651. Found :466.1633.
44		TOF MS ES^+ exact mass calculated for $C_{25}H_{22}N_6OS$ (MH+): 455.1654. Found :455.1626.
45		TOF MS ES^+ exact mass calculated for $C_{28}H_{29}N_5OS$ (MH+): 484.2171. Found :484.2133.
46		TOF MS ES^+ exact mass calculated for $C_{27}H_{27}N_5OS$ (MH+): 470.2014. Found :470.1964.

Biology

The biological activity of the compounds of the invention may be assessed using the following assays:

Assay 1 (Cellular transcriptional assay)

The potential for compounds of the invention to inhibit TGF-β signalling may be demonstrated, for example, using the following *in vitro* assay.

The assay was performed in HepG2 cells stably transfected with the PAI-1 promoter (known to be a strong TGF-β responsive promoter) linked to a luciferase (firefly) reporter gene. The compounds were selected on their ability to inhibit luciferase activity in cells exposed to TGF-β. In addition, cells were transfected with a second luciferase (Renilla) gene which was not driven by a TGF-β responsive promoter and was used as a toxicity control.

96 well microplates were seeded, using a multidrop apparatus, with the stably transfected cell line at a concentration of 35000 cells per well in 200 µl of serum-containing medium. These plates were placed in a cell incubator.

18 to 24 hours later (Day 2), cell–incubation procedure was launched. Cells were incubated with TGF-β and a candidate compound at concentrations in the range 50 nM to 10 µM (final concentration of DMSO 1%). The final concentration of TGF-β (rhTGFβ-1) used in the test was 1 ng/mL. Cells were incubated with a candidate compound 15-30 mins prior to the addition of TGF-β. The final volume of the test reaction was 150 µl. Each well contained only one candidate compound and its effect on the PAI-1 promoter was monitored.

Columns 11 and 12 were employed as controls. Column 11 contained 8 wells in which the cells were incubated in the presence of TGF-β, *without* a candidate compound. Column 11 was used to determine the 'reference TGF-β induced firefly luciferase value' against which values measured in the test wells (to quantify inhibitory activity) were compared. In wells A12 to D12, cells were grown in medium without TGF-β. The firefly luciferase values obtained from these positions are representative of the 'basal firefly luciferase activity'. In wells E12 to H12, cells were incubated in the presence of TGF-β and 500 µM CPO (Cyclopentenone, Sigma), a cell toxic compound. The toxicity was revealed by decreased firefly and renilla luciferase activities (around 50 % of those obtained in column 11).

12 to 18 hours later (day 3), the luciferase quantification procedure was launched. The following reactions were performed using reagents obtained from a Dual Luciferase Assay Kit (Promega). Cells were washed and lysed with the addition of 10 µl of passive lysis buffer (Promega). Following agitation (15 to 30 mins), luciferase activities of the plates were read in a dual-injector luminometer (BMG lumistar). For this purpose, 50 µl of luciferase assay reagent and 50 µl of 'Stop & Glo' buffer were injected sequentially to quantify the activities of both luciferases. Data obtained from

the measurements were processed and analysed using suitable software. The mean Luciferase activity value obtained in wells A11 to H11 (Column 11, TGF-βonly) was considered to represent 100% and values obtained in wells A12 to D12 (cells in medium alone) gave a basal level (0%). For each of the compounds tested, a concentration response curve was constructed from which an IC_{50} value was determined graphically.

Assay 2 (Alk5 Fluorescence Polarization Assay)

Kinase inhibitor compounds conjugated to fluorophores, can be used as fluorescent ligands to monitor ATP competitive binding of other compounds to a given kinase. The increase in depolarization of plane polarized light, caused by release of the bound ligand into solution, is measured as a polarization/anisotropy value. This protocol details the use of a rhodamine green-labelled ligand for assays using recombinant GST-ALK5 (residues 198-503).

Assay buffer components: 62.5 mM Hepes pH 7.5 (Sigma H-4034), 1 mM DTT (Sigma D-0632), 12.5 mM $MgCl_2$ (Sigma M-9272), 1.25 mM CHAPS (Sigma C-3023).

Protocol: Solid compound stocks were dissolved in 100% DMSO to a concentration of 1 mM and transferred into column 1, rows A-H of a 96-well, U bottom, polypropylene plate (Costar #3365) to make a compound plate. The compounds were serially diluted (3-fold in 100% DMSO) across the plate to column 11 to yield 11 concentrations for each test compound. Column 12 contained only DMSO. A Rapidplate™-96 was used to transfer 1 µl of sample from each well into a 96-well, black, U-bottom, non-treated plate (Costar #3792) to create an assay plate.

ALK5 was added to assay buffer containing the above components and 1 nM of the rhodamine green-labelled ligand so that the final ALK5 concentration was 10 nM based on active site titration of the enzyme. The enzyme/ligand reagent (39 µl) was added to each well of the previously prepared assay plates. A control compound (1 µl) was added to column 12, rows E-H for the low control values. The plates were read immediately on a LJL Acquest fluorescence reader (Molecular Devices, serial number AQ1048) with excitation, emission, and dichroic filters of 485nm, 530 nm, and 505 nm, respectively. The fluorescence polarization for each well was calculated by the Acquest reader and then imported into curve fitting software for construction of concentration response curves. The normalized response was

determined relative to the high controls (1 µl DMSO in column 12, rows A-D) and the low controls (1 µl of control compound in column 12, rows E-H). An IC_{50} value was then calculated for each compound

Using the above assays all Examples of the invention show ALK5 receptor modulator activity (having IC_{50} values in the range of 1 to 300 nM) and TGF-β cellular activity (having IC_{50} values in the range of 0.001 to 10 µM).

5-{2-[4-(4-Ethylpiperazin-1-yl)phenyl]pyridin-4-yl}-4-(6-methylpyridin-2-yl)-1,3-thiazol-2-amine (Example 3) showed an ALK5 receptor modulator activity of 14 nM and TGF-β cellular activity of 29 nM.

4-[2-(4-((Dimethylamino)methyl)phenyl)pyridin-4-yl]-5-[6-methylpyridin-2-yl]-1,3-thiazol-2-amine (Example 25) showed an ALK5 receptor modulator activity of 29 nM and TGF-β cellular activity of 31 nM.